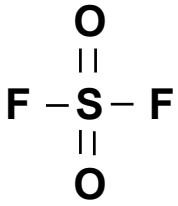
SULFURYL FLUORIDE (Vikane®)

RISK CHARACTERIZATION DOCUMENT



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August 26, 2004

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Acknowledgment:
A draft (March 16, 2004) was reviewed by the Office of Environmental Health Hazard Assessment and the Air Resources Board of the California Environmental Protection Agency

Table of Contents

List of Tables

I. TECHNICAL SUMMARY

I. Introduction

Sulfuryl fluoride (Vikane®) is a fumigant registered for structural and non-food commodity fumigations in California. This comprehensive risk assessment focused on the current registered uses of sulfuryl fluoride and was conducted under the mandates of the Birth Defect Prevention Act (SB 950) and Toxic Air Contaminant Act (AB 1807). Potential exposure to sulfuryl fluoride and fluoride in the diet from the use of sulfuryl fluoride in food commodity fumigation will be assessed when the food-use registration is evaluated in California.

II. Toxicology Profile

A pharmacokinetic study in rats given sulfuryl fluoride by inhalation showed that about 18% of the administered dose was absorbed. Peak plasma level was measured immediately after exposure, with the alpha phase half-life of 1 to 2 hours. The respiratory tract contained the highest level of radioactivity; lower levels were detected in the kidneys, brain, spleen, and other tissues. The primary route of excretion was via the urine (about 80% of the absorbed dose).

For acute toxicity, the lethal concentrations for 50% lethality (LC_{50}) in rats were 3020-3730 ppm for 1-hour exposure and 991-1500 ppm for 4-hour exposure. The 4-hour LC_{50} in mice was >400 ppm to 660 ppm. At non-lethal concentrations, neurotoxicity was observed in rats, mice, rabbits, and dogs. With acute to 2 weeks of exposures, clinical signs observed in these species included tremors, lethargy, respiratory effects, incapacitation, tetany, and convulsion. At the lowest-observed effect level, animals treated with sulfuryl fluoride for two weeks showed tissue damage in the kidney (rats), brain (rabbits, mice), and respiratory tract (rabbits and dogs). After 13 weeks of inhalation exposure, the brain was the primary target for sulfuryl fluoride toxicity in all species studied (rats, mice, rabbits, and dogs). The most common lesion was vacuoles in the cerebrum. Other effects reported were nasal tissue inflammation (rats and rabbits), kidney hyperplasia (rats), lung histiocytosis (rats), thyroid hypertrophy (mice), and fluorosis (rats). After chronic exposure, the primary target tissue for sulfuryl fluoride was the brain and the respiratory tract in rats, mice, and dogs. As with subchronic exposure, brain vacuoles were observed in the cerebrum. The lesions in the respiratory tract included nasal tissues, trachea, larynx, and lungs. Dental fluorosis was observed in both rats and dogs. Progressive glomerulonephropathy was considered the cause of death in sulfuryl fluoride treated rats. Sulfuryl fluoride was not oncogenic in rats, mice, and dogs.

Sulfuryl fluoride was not genotoxic in either *in vitro* or *in vivo* studies. As for reproductive toxicity, sulfuryl fluoride caused lung (macrophage aggregates, chronic inflammation) and brain (vacuolation) lesions in the adults and reduced pup body weights in rats. There were no teratogenic effects in rats or rabbits exposed to sulfuryl fluoride during gestation. The only fetal effect observed was reduced fetal body weight in rabbits, but not in rats. Maternal toxicity was limited to reduced body weights.

III. Risk Assessment

Hazard Identification

The critical acute No-Observed-Effect Level (NOEL) for sulfuryl fluoride was 300 mg/kg/day (300 ppm, absorbed dose 54 mg/kg/day) for no effects in Functional Observational Battery or electrophysiological responses in rats after two days of exposure. For exposures of 1-2 weeks, the critical NOEL was 40 mg/kg/day (100 ppm, absorbed dose 7.2 mg/kg/day) for malacia and vacuoles in the cerebrum of rabbits exposed to 300 ppm. For subchronic inhalation exposure (13-weeks), the critical NOEL was 12 mg/kg/day (30 ppm, absorbed dose 2.2 mg/kg/day) for brain vacuoles in rabbits. With chronic exposure, respiratory system effect (lung pathology and alveolar macrophage aggregates) was the sensitive endpoint; the critical NOEL was 4 mg/kg/day (5 ppm, absorbed dose 0.72 mg/kg/day) in rats. Since there was no evidence of sulfuryl fluoride oncogenicity, cancer potency factors were not calculated.

For the occupational exposures (adults), the reference concentrations were 2.57 ppm (10.72 mg/m^3), 0.48 ppm (2.01 mg/m^3), 0.14 ppm (0.60 mg/m^3), and 0.04 ppm (0.18 mg/m^3) for acute, 1-2 week, subchronic, and chronic exposures, respectively. The reference concentrations for residential and bystander exposures (represented by infants and children) were 0.14 ppm (0.59 mg/m^3), 0.026 ppm (0.11 mg/m^3), 0.008 ppm (0.03 mg/m^3), and 0.002 ppm (0.01 mg/m^3) for acute, 1-2 week, subchronic, and chronic exposures, respectively.

Exposure Assessment

At the submaximal application rate, fumigator's short-term exposures for individual fumigation activities ranged from 0.000006 mg/kg/day (closing of structure) to 0.029 mg/kg/day (introducing fumigant). The combined (fumigation and tenting activities) short-term exposures were 0.0377 mg/kg/day (all fumigator activities) and 1.1699 mg/kg/day (fumigator and tent crew activities). The short-term exposures of the tent crew ranged from 0.0404 mg/kg/day (ground snake removal) to 1.1322 mg/kg/day (general detarping). For repeated exposures, the intermediate exposures ranged from 0.000002 mg/kg/day (closing structures) to 0.311 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.0131 mg/kg/day (ground snake removal) to 0.2912 mg/kg/day (general detarping) for the tent crew. The annual exposures ranged from 0.0000008 mg/kg/day (closing structures) to 0.154 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.0065 mg/kg/day (ground snake removal) to 0.1433 mg/kg/day (general detarping) for the tent crew. The lifetime exposures ranged from 0.0000004 mg/kg/day (closing structures) to 0.0821 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.0034 mg/kg/day (ground snake removal) to 0.0765 mg/kg/day (general detarping) for the tent crew. At the maximal application rate, the exposures were 14.5 times that of the submaximal rate for all exposure groups. For handlers in non-food commodity fumigation, the acute, annual, and lifetime exposures were the 0.429 mg/kg/day, 0.001 mg/kg/day, and 0.001 mg/kg/day, respectively.

Acute exposures of residents returning to homes after clearance for occupation ranged from 0.20 mg/kg/day (15-18 years old) to 0.52 mg/kg/day (1-2 years old). The range of short-

term exposures was 0.05 mg/kg/day (12-18 years) to 0.12 mg/kg/day (1-2 years old). The range of annual exposures was 0.0009 mg/kg/day (15-18 years) to 0.0024 mg/kg/day (1-2 years old). The lifetime exposure for adults was 0.0002 mg/kg/day.

Bystander exposures to structural fumigation ranged from 0.14 mg/kg/day (15-18 years old) to 0.34 mg/kg/day (1-2 years old) during the first 12-hours of fumigant application at submaximal rate. The 24-hour overall exposures were 0.2 mg/kg/day (15-18 years old) to 0.48 mg/kg/day (1-2 years old). The annual exposures (1 day per year) ranged from 0.0006 mg/kg/day (12-18 years old, adult) to 0.0013 mg/kg/day (1-2 years old). The lifetime exposure of adults was 0.0002 mg/kg/day. The exposures for maximal application rate were 10 times that of the submaximal rate. Using the TRAP method for aeration after submaximal application rate, the acute 2-hour exposures of bystanders ranged from 0.36 mg/kg/day (15-18 years old) to 0.85 mg/kg/day (1-2 years old). The annual exposures ranged from 0.001 mg/kg/day (12 years old to adult) to 0.002 mg/kg/day (all less than 12 years old). The lifetime exposure of adults was 0.0002 mg/kg/day. The exposures for maximal application rate were 14.5 times that of the submaximal rate. Using the Stack plan for aeration after submaximal application rate, the acute 1-hour exposures for bystanders ranged from 0.05 mg/kg/day (15-18 years old) to 0.13 mg/kg/day (1-2 years old). For the 4-hour exposure period, the acute exposures ranged from 0.06 mg/kg/day (15-18 years old) to 0.14 mg/kg/day (1-2 years old). The annual exposures ranged from 0.00016 mg/kg/day (15-18 years) to 0.00038 mg/kg/day (1-2 years old). The lifetime exposure of adults was 0.00005 mg/kg/day. The exposures for maximal application rate were 10 times that of the submaximal rate.

For non-food commodity fumigation, the bystander acute 24-hour exposures ranged from 0.89 mg/kg/day (15-18 years old) to 2.10 mg/kg/day (1-2 years old). The annual exposures ranged from 0.0024 mg/kg/day (15-18 years old) to 0.0058 mg/kg/day (1-2 years old). The lifetime exposure of adults was 0.002 mg/kg/day.

Risk Characterization

The acute NOEL was used to address the daily exposures (short-term exposures) of the fumigators and tent crews and acute exposures of residents and bystanders of the structural fumigation as well as handlers and bystanders to non-food commodity fumigation. The short-term exposures of fumigators and tent crews were also assessed using a 1-2 week NOEL. Intermediate and annual exposures (more than 7 days per year) for these workers were assessed using subchronic and chronic NOELs, respectively. The lifetime risk of sulfuryl fluoride exposure for all groups was not evaluated since sulfuryl fluoride has not been shown to be oncogenic in either humans or experimental animals. The potential risk from exposure to sulfuryl fluoride was evaluated by comparing the margins of exposure to benchmarks. The benchmarks were 100 and 1000 for occupational and residential/bystander exposures, respectively. For AB 1807, bystander exposures exceeding 1/10 of the reference concentration would be considered for listing as a toxic air contaminant. This criterion is equivalent to a MOE of at least 10,000 for bystander exposures.

For structural fumigation using the submaximal rate of application, the MOEs for

individual fumigator activities for all durations were greater than 100. For total fumigator activities, the MOEs were greater than 100, except 67 for chronic exposure. All MOEs for workers doing both fumigation and tent crew activities were less than 100. For the tent crew, the acute and 1-2 week MOEs were higher than 100 (range from 130 to 1337) for most activities, except for general detarping, ground seam opening, and roof seam opening where the MOEs were 6 to 48. For subchronic exposure, the MOEs ranged from 8 (general detarping) to 168 (ground snake removal). For chronic exposure, the MOEs ranged from 5 (general detarping) to 111 (ground snake removal). At the maximal rate, the MOEs for fumigators and tent crew were generally less than 100 except for scenarios with minimal exposures such as opening, closing, and testing activities for fumigators. For handlers of non-food commodity fumigation, the MOE was 126 for acute exposure.

For residents reoccupying fumigated homes after clearance, the acute MOEs ranged from 104 (1-2 years old) to 180 (9-11 years old) for younger children. For the older children and adults, the acute MOEs ranged from 225 (adults) to 270 (15-18 years old).

For bystander exposures during submaximal application rate, the acute (first 12-hours) MOEs for bystanders ranged from 159 (1-2 years old) to 386 (15-18 years old). The MOEs for 24-hour exposure during the application phase ranged from 113 (1-2 years old) to 270 (15-18 years old). At the maximal application rate, the acute and short-term MOEs for all age groups were at or less than 38. During aeration using the TRAP method after application at the submaximal rate, the short-term MOEs for the bystanders ranged from 64 (1-2 years old) to 150 (15-18 years old). For aeration using the Stack method, the acute MOEs for the first hours ranged from 415 (1-2 years old) to 1080 (15-18 years old). Over the 2-hour period, the MOEs ranged from 386 (1-2 years old) to 900 (15-18 years old). At the maximal application for either aeration methods, the acute MOEs were all less than 100. The acute MOEs for bystanders near a commodity fumigation facility ranged from 26 (1-2 years old) to 61 (15-18 years old).

IV. Risk Appraisal

The uncertainties associated with the selection of the endpoints and the NOELs are due to limitations in the study design of the toxicity studies and information regarding the mechanism of toxicity. There were also uncertainties associated with the exposure estimates. Sources of under- and over-estimation of exposures include monitoring samples analysis, assumptions regarding use of Self-Contained Breathing Apparatus, application rate, frequency of use, and durations of exposure.

There was a large range of MOEs for workers depending on work activities. The MOEs for opening and closing structures were greater than 10,000, while they were less than 100 for some fumigator and tent crew activities. For adult residential exposures to structural fumigation (reentry, application, and aeration) at submaximal application rates, the acute MOEs for peak sulfuryl fluoride periods were generally greater than 100. However, the MOEs for young children were about 100, much less than the 1000 benchmark. For bystanders to non-food commodity fumigation, the MOEs were all less than 100. These were based on the assumption of 24 hours of continuous exposures at 5 ppm. Since the bystander exposures exceeded 1/10 of the

reference concentrations, sulfuryl fluoride met the listing criteria and will be reviewed by the Scientific Review Panel for AB 1807.

V. Issues Related to the Food Quality Protection Act

With respect to the Food Quality Protection Act issues, there was no evidence for potential increased sensitivity by infants and children to the prenatal and post-natal toxicity of sulfuryl fluoride. There is a concern for potential developmental neurotoxicity in humans exposed to sulfuryl fluoride, which caused vacuoles in the adult brain after repeated exposures and in multiple species. In the absence of a developmental neurotoxicity study, an additional ten-fold factor was included in the reference concentration calculation for residents/bystanders, and margins of exposure considerations. There may be aggregate exposures of sulfuryl fluoride and fluoride from multiple exposure routes and this would be addressed in the dietary risk assessment document for ProFume®. There is a potential for cumulative toxicity of fluoride from sources such as drinking water, cryolite, sulfuryl fluoride, and fluoride supplemented consumer products. The current database did not show sulfuryl fluoride to cause endocrine disruption effects.

VI. Conclusion

The human health risk associated with the use of sulfuryl fluoride in structural and non-food commodity fumigation was evaluated in this Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals: neurotoxicity in rats and rabbits for acute, 1-2 week, and subchronic exposures, and lung pathology in rats for chronic exposure. The primary route of exposure was inhalation for workers, residents, and bystanders. Estimated human exposures were evaluated in terms of margins of exposure, and a comparison with the reference concentrations to determine the scenarios of potential health concern. The estimated acute exposures for bystanders exceeded 1/10 of the reference concentrations, thus would meet the criteria for listing under the AB 1807 Toxic Air Contaminant Act. The MOEs for the following tasks and exposure duration did not meet the benchmark of 100 for occupational (adult) exposure or 1000 for residential and bystander exposures:

1. Structural fumigation:

a. Workers at submaximal application rate: total fumigator activities (chronic), fumigator and tent crew tasks (all durations), ground seam opening (1-2 week, subchronic and chronic), roof seam opening (1-2 week, subchronic and chronic), tarpaulin folding (chronic), and general detarping (all durations).
b. Workers at maximal application rate: introducing fumigant (1-2 week, subchronic, and chronic), total fumigator activities (1-2 week, subchronic, and chronic), fumigator and tent crew tasks (all durations), and all tent crew activities (all durations).
c. Residents following clearance: all age groups (acute).
d. Bystanders during application phase: all age groups (submaximal and maximal rate application, acute 12-hour and 24-hour).
e. Bystanders during TRAP method of aeration: all age groups (submaximal and maximal

rate application, acute 2-hour).
f. Bystanders during Stack method of aeration: all age groups, except 15-18 years (submaximal rate application, acute 1-hour), and all age groups (submaximal rate application, acute 4-hour; maximal rate application, acute 1-hour and 4-hour).

2. Non-food commodity fumigation: all bystanders (acute 24-hour).

The potential for health concerns in these scenarios should be viewed in the context of the limitations and uncertainties discussed. The toxicology database, while complete with respect to registration requirements in California, did not include a developmental neurotoxicity study. This study would be helpful to determine the neurotoxicity potential of sulfuryl fluoride in infants and children. The assumption in this Document was that the NOEL would be 10-fold lower than the critical NOELs. Additional acute toxicology studies with shorter observation periods or declining doses could better characterize the potential toxicity associated with some fo the exposure scenarios. Additional exposure data, in particular those with maximal application rate and for commodity fumigation, are needed to better estimate actual exposures. Furthermore, expanded uses such as food commodity fumigation could result in higher exposures and lower margins of exposures. This aspect should be considered in the regulation of this use and future uses.

II. INTRODUCTION

A comprehensive human health risk assessment on current use of sulfuryl fluoride (Vikane®) in structural and non-food commodity fumigation was conducted because of adverse effects identified in chronic and oncogenicity studies submitted under The Birth Defect Prevention Act of 1984 (SB 950). This assessment was also conducted because sulfuryl fluoride is a candidate for consideration as a toxic air contaminant under the Toxic Air Contaminant Act (AB 1807). Potential exposure to sulfuryl fluoride and fluoride in the diet from the use of sulfuryl fluoride in food commodity fumigation will be assessed when the food-use registration is evaluated in California. This latter assessment will also take into consideration of findings of the National Academy of Sciences, if available, which is currently reviewing the regulatory levels for fluoride, a metabolite of sulfuryl fluoride[1].

II.A. CHEMICAL IDENTIFICATION

Sulfuryl fluoride (sulfuric oxyfluoride) is a fumigant used for structural and commodity fumigations. Its insecticidal activity was first reported in 1956 for drywood termites and other insects (Kenaga, 1957; Doty and Kenaga, 1962). It is non-flammable, non-corrosive, and odorless (Stewart, 1957). As an insecticide, sulfuryl fluoride disrupts carbohydrate and lipid metabolism in termites (Meikle *et al*., 1963). Fluoride ion is considered the active metabolite; it inhibits lipase and other enzymes in the glycolysis cycle and increases oxygen uptake in treated termites. The termite dies when protein and amino acids, as energy sources, are depleted. Sulfuryl fluoride also inhibits metabolic processes in locus and mealworm eggs (Outram, 1970).

In humans, acute inhalation exposure to high concentrations of sulfuryl fluoride results in respiratory irritation, pulmonary edema, nausea, abdominal pain, central nervous system depression, numbness in the extremities, muscle twitching, seizures, and death (U.S. Environmental Protection Agency; U.S. EPA, 1999a). Proteinuria and azotemia may be associated with renal injury (U.S. EPA, 1999a). Case reports are presented in **III.I. HUMAN EXPOSURE**. The mechanism of sulfuryl fluoride toxicity in mammals is unknown. Fluoride ion may affect muscle activity (muscle twitching, seizures) by binding to calcium (Scheuerman, 1985). Other effects may be attributed to its binding to potassium and magnesium ions. Direct contact of the skin to concentrated sulfuryl fluoride as a liquid causes tissue damage to eyes, mucous membranes, or skin (U.S. EPA, 1985a).

[1] In 2003, the U.S. EPA Office of Water requested the National Academy of Sciences (NAS) to evaluate the scientific and technical basis of the fluoride levels in the drinking water. The NAS will advise the U.S. EPA on the adequacy of its fluoride Maximum Contaminant Level (MCL) and Secondary Maximum Contaminant Level (SMCL) to protect children and others from adverse effects. The NAS will determine the relative contribution of various fluoride sources (*e.g*., food, dental-hygiene products) to total exposure, and determine data gaps and make recommendations for future research relevant to setting the MCL and SMCL for fluoride.

II.B. REGULATORY HISTORY

II.B.1. U.S. EPA and California Regulations

Sulfuryl fluoride was first registered as a pesticide for structural fumigation in 1959 (U.S. EPA, 1993a and b). In 1985, the U.S. EPA issued a reregistration guidance document for sulfuryl fluoride (U.S. EPA, 1985b). For reregistration, residue studies for sulfuryl fluoride and degradation products in the air and representative food and non-food articles were required because of concerns about human exposure to residues on fumigated household articles. Label changes were required to include removal or sealing of edible items prior to fumigation, classification as a restricted use pesticide, precautionary statements for humans and ecological effects, inclusions of chloropicrin use directions if applicable, and respiratory protection equipment for applicators. There was no requirement for environmental fate data because sulfuryl fluoride uses were "strictly" indoor uses and it dissipated into the atmosphere after use. The requirement of additional toxicology data was contingent upon the determination of residues on household items.

In 1993, U.S. EPA issued the Reregistration Eligibility Document (RED) for sulfuryl fluoride (U.S. EPA, 1993b). The RED concluded that the existing reentry level of 5 ppm did not provide sufficient margin of exposure (MOE) and needed to be lowered to 2 ppm for adults and 1 ppm for children. The registrant was allowed to submit additional data on residue dissipation for further assessment of the reentry level. Workers were required to wear a NIOSH-approved, self-contained breathing apparatus (SCBA) upon reentry regardless of the sulfuryl fluoride air concentration. The U.S. EPA also determined that the workers may have subchronic and chronic exposures to sulfuryl fluoride and required the submission of a 90-day inhalation neurotoxicity study in rats. Label changes were needed to include more directions on the use of chloropicrin, fact sheets for adult occupants, and incorporation of an environmental hazard statement. To date, the reentry level on the label remained at 5 ppm. There is no requirement for SCBA for reentry.

In 2002, U.S. EPA issued temporary tolerances for the use of sulfuryl fluoride (ProFume®) in post-harvest fumigation of walnuts and raisins (U.S. EPA, 2001a and 2002a). The temporary tolerances were needed to support a 3-year experimental use permit (EUP) effective from 2002 to 2005. However, this EUP was never used because the California Department of Pesticide Regulation (DPR) did not issue the necessary state authorization for the EUP to proceed. This EUP was withdrawn when Dow Chemical Company submitted a petition to the U.S. EPA for the establishment of tolerances of sulfuryl fluoride and fluoride residues on dried fruits, nuts, and grains (U.S. EPA, 2002b). U.S. EPA recently granted permanent tolerances for these uses (U.S. EPA, 2004a). In the risk assessment for the registration of post-harvest food use, U.S. EPA noted that the Food Quality Protection Act (FQPA) factor (also referred to as the Special FQPA safety factor) to address potential increased sensitivity of infants and children was not needed (U.S. EPA, 2004 b and c). However, the database showed that sulfuryl fluoride is a neurotoxicant and a developmental neurotoxicity study was necessary. In the absence of such a study, the U.S. EPA applied a 10-fold FQPA safety factor (also referred to as the default FQPA safety factor) for the reference concentrations for chronic dietary exposure and repeated residential exposures. This FQPA mandated factor was retained since available data did not

provide basis to support the reduction or removal of such a factor.

The U.S. EPA considered the residue chemistry databases for sulfuryl fluoride and fluoride ion as "marginally adequate" since the available studies focused on the effect of fumigation conditions and not on residues resulting from proposed label directions. No worker or residential exposure data for commodity (food) fumigation use were submitted; U.S. EPA assumed that bystander exposure from grain processing facilities would not be of concern based on the following assumptions: (1) fumigation of grains is infrequent and the facilities are distant from residential areas, and (2) methyl bromide buffer zones used currently by the facilities would be adequate for sulfuryl fluoride. The U.S. EPA expressed concerns regarding bystander exposure from tree nut and dried fruit fumigation facilities. Since there was no worker monitoring data, occupational exposure to ProFume® was assumed at 1 ppm, the maximum limit on the label. Because of above inadequacies in the database, the U.S. EPA set conditions for the registration of ProFume®. These included the revision of the assessment after the NAS review of the fluoride MCL and SMCL in the water, and the submission of studies on developmental neurotoxicity, residues on fumigated commodities, and worker and resident exposures.

In California, only Vikane® is registered for use in structural and non-food commodity fumigation. With respect to other regulatory actions in California, sulfuryl fluoride is a candidate for consideration as a toxic air contaminant under AB 1807, the Toxic Air Contaminant Act. Sulfuryl fluoride is not listed under Proposition 65, the Safe Drinking Water Act because it is not considered a developmental/ reproductive toxicant or a carcinogen.

II.B.2. Regulatory Limits and Standards

In establishing permanent tolerances for the use of sulfuryl fluoride in food commodities (U.S. EPA, 2004a), current U.S. EPA reference concentrations for sulfuryl fluoride are listed below. Additional discussion on these reference concentrations is under **IV.D.1. Hazard Identification and Reference Concentrations**.

- Short-term exposure: 0.30 mg/kg/day (workers), 0.030 mg/kg/day (residents)
- Intermediate-term exposure: 0.085 mg/kg/day (workers), 0.0085 mg/kg/day (residents)
- Long-term exposure: 0.03 mg/kg/day (workers), 0.003 mg/kg/day (residents)

The Occupational Safety and Health Administration permissible levels are: Permissible Exposure Level (PEL) of 5 ppm (20 mg/m^3) as an 8-hour time-weighed average, and a Short-Term Exposure Level (STEL) of 10 ppm. The National Institute for Occupational Safety and Health set the same levels for Recommended Exposure Limit (REL) of 5 ppm and STEL of 10 ppm. The Immediately Dangerous to Life or Health Concentration (IDLH) is 200 ppm. The American Conference of Government Industrial Hygienists (ACGIH) Threshold Limit Values (TLV®) and STEL are 5 ppm and 10 ppm, respectively.

For fluoride, the U.S. EPA maximum contaminant level goal (MCLG) and secondary maximum contaminant level (SMCL) are 4 mg/L and 2 mg/L, respectively, in the drinking water

(U.S. EPA, 2004a). The California MCL is 1.4 to 2.4 mg/L, depending on the ambient temperature (California Health and Safety Code, Title 22 as cited in OEHHA, 1997). The Office of Environmental Health Hazard Assessment established a public health goal (PHG) of 1 ppm or 1 mg/L for the protection of dental fluorosis in children (OEHHA, 1997).

II.C. TECHNICAL AND PRODUCT FORMULATIONS

Vikane® is the only registered product in California. It is used to control a variety of pests such as drywood termites, powder post beetles, old house borers, bedbugs, clothes moths, rodents, and cockroaches in dwellings, buildings, construction materials, furnishings, and vehicles. Since Vikane® is odorless and colorless, chloropicrin is required as a warning agent at (1 oz/10,000-15,000 ft^3 or 0.07-0.1 g/m^3 of space to be fumigated) and is introduced at least 5 to 10 minutes prior to the introduction of Vikane into the site. The U.S. EPA has recently registered the use of ProFume® for food commodity fumigation (U.S. EPA, 2004a), but this use has yet to be approved in California.

II.D. USAGE

From 1994 to 2002, sulfuryl fluoride use increased from 1.7 million pounds to 3 million pounds per year in California (DPR, 2004). The major use is for structural pest control (>99% of total use) and the increase is attributed to the decline in the use of methyl bromide for the same purpose. Other uses accounted for <1 % of the total and include landscape maintenance, rights of way, and commodity (non-food) fumigation.

II.E. ILLNESS REPORTS

Between 1997 and 2001, there were 32 cases reported to the DPR's Pesticide Illness Surveillance Program (DiPaolo and Beauvais, 2004; **Appendix A**). These cases may be associated with either sulfuryl fluoride, chloropicrin, or in combination, due to spillage, drift, and residues. Individuals with short-term exposures complained of eye (burning, water), nose (irritated), throat (coughing, dry), and respiratory (difficulty in breathing, shortness of breath) problems (Mehler, 2001). Some also reported nausea, dizziness/light headedness, numbness of hands, disorientation, headache, confusion, and memory loss. People have died from entering houses before clearance for entry. Published case reports of sulfuryl fluoride exposures are presented in section **III.I. HUMAN EXPOSURE**.

II.F. PHYSICAL AND CHEMICAL PROPERTIES

Chemical name:	Sulfuryl fluoride
CAS Registry number:	2699-79-8
Common name:	Sulfuryl fluoride
Trade name:	Vikane®, ProFume® (not yet approved for California use)
Molecular formula:	F_2O_2S
Molecular weight:	102.07 g/mole
Chemical structure:	F_2-S-O_2
Physical appearance:	Odorless, colorless gas at 25EC
Solubility:	0.075 g/100 g water, 0.78 g/100 ml Wesson oil, 1.74 g/100 ml acetone, 2.12 g/100 ml chloroform
Boiling point:	-55.21EC at 760 mm Hg
Melting point:	-135.67EC at 760 mm Hg
Vapor pressure:	9150 mm Hg at 10EC; 13,442 mm Hg at 25EC
Specific gravity:	1.342 for liquid at 25EC compared to water at 4EC 3.52 for the gas compared to air
Octanol:Water partition coefficient:	2.57
Henry's Law constant (K_b):	3.28 x 10-2 atm-m^3/mol
Conversion factor:	1 ppm=4.17 mg/m^3

a/ References: Torkelson, *et al*., 1966; U.S. EPA, 1985 a and b, 1993 a and b; Rick *et al*., 2000; Farm Chemicals Handbook, 2001; The Merck Index, 1996; Kenaga, 1957. Octanol-water coefficient and Henry's Law constant were from **Appendix B**.

II.G. ENVIRONMENTAL FATE

Summary: Sulfuryl fluoride is hydrolyzed in water with release of fluoride ion. During structural and commodity fumigation, it is released into the air and binds to food components when the food items are not sufficiently sealed.

II.G.1. Environment

There is little information on the ecological effect and environmental fate of sulfuryl fluoride. The U.S. EPA waived these types of studies because they are difficult to conduct when the test compound is a gas at ambient temperature (U.S. EPA, 1993b). Sulfuryl fluoride is released into the air when used in structural and commodity fumigation. When in contact with water, sulfuryl fluoride is hydrolyzed slowly under neutral conditions, but rapidly under alkaline conditions. The environmental fate of sulfuryl fluoride is included in **Appendix B**.

II.G.2. Residues from Structural Fumigation

In response to the U.S. EPA requirement for residue data as part of the reregistration process (U.S. EPA, 1985b), several studies were conducted to determine if sulfuryl fluoride residues remained on household items after structural fumigation. The current label has food and closure requirements to minimize food contamination with sulfuryl fluoride during structural fumigation. In a laboratory study, sulfuryl fluoride residues were found in food items after fumigation with sulfuryl fluoride (36 mg/L or 360 mg/L) for 20 hours (Osbrink *et al*., 1988 and Scheffrahn *et al*., 1987). The items were in cups (except for apples and wrapped snack cakes) and were either uncovered, wrapped in one-layer, or two-layers of polyethylene films during fumigation. The films offered at least 79% and 96% of protection for one- and two-layers, respectively. Of the food items tested, highest levels of sulfuryl fluoride were detected in oil and lowest in powdered milk (Table 1). At 36 mg/L sulfuryl fluoride and after 2 hours of aeration, 23720 ppb, 4619 ppb, and 746 ppb of sulfuryl fluoride were detected in oil samples with none, 1-layer, and 2-layer of films, respectively. At the same sulfuryl fluoride rate, 5.4 ppb, 0.4 ppb, and 0.1 ppb of sulfuryl fluoride were detected in powdered milk for none, 1-layer, and 2-layer of films, respectively. With aeration of 2 hours and up to 960 hours, desorption half-life depended on the food item, fumigation concentration, and layers of polyethylene film. The half-life was generally shorter for items with lower initial concentration and density. For example in the 36 mg/L sulfuryl fluoride samples, the half-lives were about 3 hours for dog food and 8.06 to 11.36 hours for cake, compared to 13.86 to 31.51 hours for oil.

The potential for sulfuryl fluoride residues in food stored on shelves or in freezers housed inside fumigated structures such as homes were examined in several studies. Scheffrahn *et al* (1989a) showed fluoride residues in frozen foods stored in a freezer during fumigation with sulfuryl fluoride (36 mg/L or 360 mg/L) for 20 hours and aeration for 5 minutes. For the two rates of sulfuryl fluoride, the corresponding fluoride residues in the uncovered food items were: 2.5 ppm and 66.1 ppm for beef, trace and 17.8 ppm for French fries, trace and 19.2 ppm for peas, 0.9 and 25.7 ppm for ice cream, and 5.9 and 89.7 ppm for flour.

Table 1. Effect of polyethylene film and the dissipation of sulfuryl fluoride residues from food or medicine.

Item	Layers of polyethylene film	Concentration (ppb) after 2 hours of aeration		Half-life (hours)	
		36 mg/L SF	360 mg/L SF	36 mg/L SF	360 mg/L SF
Oil	0	23720	256446	31.51	57.77
	1	4619	22431	14.44	63.02
	2	746	4371	13.86	38.51
Flour	0	174	6672	22.36	57.77
	1	13	59	10.19	99.03
	2	1	10	7.62	36.48
Beef	0	134	ND	22.36	ND
	1	10		5.93	
	2	0.9		NA	
Acetamino-phen	0	17	682	20.39	49.51
	1	3.5	29	13.08	36.48
	2	0.3	8.7	NA	28.88
Apple	0	4092	69629	12.60	11.95
	1	70	4176	NA	13.59
	2	2	402	NA	3.03
Cake	0	218	ND	11.36	ND
	1	25		8.06	
	2	0.5		NA	
Dog food	0	750	ND	3.71	ND
	1	134		3.26	
	2	28		3.15	
Powdered milk	0	5.4	ND	NA	ND
	1	0.4			
	2	0.1			

a/ Data from Osbrink *et al*., 1988. SF=sulfuryl fluoride, NA=not enough data point to calculate, and ND=not fumigated at this rate. The half-life was not determined for powdered milk because only two aeration times (2 and 8 hours) were studied due to the low residues.

In a similar study with longer aeration time, fluoride and sulfate residues were measured in 8 food items left on shelves during fumigation and aerated for 1, 8, or 15 days (Scheffrahn *et al.*, 1989b and 1987). There was essentially no change in the residue levels indicating that these ions were bound to the commodities. Higher fluoride and sulfate levels were found in dried beef and dry milk than in apple, cake, dog food, flour, acetaminophen and oil. No measurable fluoride and sulfate residues were found in the oil samples, which contained relatively high levels of sulfuryl fluoride detected in another study (Osbrink *et al*., 1988).

To test the effectiveness of bags to block sulfuryl fluoride entry into food, samples of

frozen food (ground beef, French fries, peas, ice cream, and flour) were either uncovered or sealed inside polyethylene Ziploc bags (Scheffrahn, 1990a). They were placed inside a freezer (-20°C) in a fumigation chamber and fumigated for 20 hours at 727 and 6803 mg sulfuryl fluoride·h/liter. After fumigation, the samples were extracted and analyzed for fluoride (quantitation limit of 0.8 ppm). No fluoride residues were found in any of the bagged samples. Fluoride residues found in uncovered samples were trace (French fries and peas) to 5.9 ppm (flour), and 17.8 (French fries) to 89.7 ppm (flour) for sulfuryl fluoride treatments of 727 mg·h/liter and 6803 mg·h/liter, respectively.

In another study, bags of different films and closures were filled with sulfuryl fluoride (5.4, 36, or 360 mg/L) to determine the protectiveness of the bags (Scheffrahn, 1990b). The concentrations corresponded to ca. 1.5, 10, or 100 times the field rate for drywood termite control. The closures from highest to lowest protection of leakage were: twist tie, heat seal, knot, masking tape, and Ziploc. Of the different types of bags, those made with nylon and nylon-containing film provided greater protection against sulfuryl fluoride penetration through the bags than those with polyethylene only.

Additional studies by Scheffrahn *et al* (1994) confirmed that nylon film bags provided more protection than polyethylene bags from sulfuryl fluoride entering the food during fumigation. Thirteen food items were placed either in a cupboard (22°C) or in a refrigerator (3°C) in a fumigation chamber and exposed to either 780 (refrigerated)/742 (cupboard) or 6113 (refrigerated)/6582 (cupboard) mg·h/L sulfuryl fluoride for 20 hours. After 2 hours of aeration, sulfuryl fluoride residues in the nylon film bags were 0 to 5.6 ppb (refrigerated) and 0 to 1.0 ppb (cupboard). Those in the polyethylene bags were 7.7 to 23.1 ppb (refrigerated) and 1.1 to 20.3 ppb (cupboard). The residue levels were further lowered with 6 hours of aeration and the reduction was greater for cupboards (6-10 fold) than the refrigerator (2-fold) samples.

The effect of manufacturer-packaging was also studied with store-bought items (Scheffrahn *et al*., 1992). Each item was fumigated with 8810 ppm sulfuryl fluoride for 20 hours. Sulfuryl fluoride entered into food via diffusion through air channels in closures (reclosed peanut butter jar) or porous packaging (Parmesan cheese), and polymer permeation (polyurethane bagged foods). Factory sealed polyethylene terephthalate (PETE) containers, Barex (an acrylonitrile and butadiene copolymer) packaging, and vacuum-packaging provided good protection with low (or zero) residues in the food items. High residues were found in food with un-sealed packaging such as reclosed peanut butter (7.6 ppm) and Parmesan cheese (0.237 ppm).

III. TOXICOLOGY PROFILE

The toxicological database of sulfuryl fluoride consisted mainly of inhalation toxicity studies because inhalation is the primary route of exposure. U.S. EPA evaluated the acute toxicity database and assigned a Toxicity Category I for acute inhalation toxicity (Lewis, 1999). U.S. EPA considered the submitted acute oral study as unacceptable and a Toxicity Category II was assigned. The U.S. EPA waived other acute toxicity studies based on considerations of the physical chemical properties and acute inhalation toxicity of sulfuryl fluoride. The assigned toxicity categories and studies were Category I for primary eye irritation, Category IV for acute dermal toxicity, Category IV for primary dermal irritation, and non-sensitizer for skin sensitization.

In the review of the toxicity studies, the acceptability of the toxicology studies (except genotoxicity studies) by DPR, where noted in this document, was based on the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies was based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). A study was considered supplemental information if the data requirement under The Birth Defect Prevention Act of 1984 (SB 950)[2] for a certain study type was fulfilled by an acceptable study or if the study was not part of the data requirement. The toxicology summary for the studies is included in **Appendix C**. The no-effect levels in these studies may be expressed as No-Observed-Effect Levels (NOELs) or No-Observed-Adverse-Effect Levels (NOAELs). For the purpose of this document, endpoints under either designation were considered relevant for hazard identification. NOELs for acute, 1-2 weeks, subchronic (13 weeks), and chronic exposures were identified. Summary tables for selected toxicity studies considered for critical NOELs and lowest-observed-effect levels (LOELs) for hazard identification are presented in Tables 4, 10, and 14 for acute, subchronic, and chronic exposures, respectively. When available, the NOAELs established by the U.S. EPA (U.S. EPA, 2004b) are also included in the study summaries.

In the conversion of ppm to mg/kg/day doses, the nominal concentrations in ppm were used since they were almost the same as the measured concentrations. The equation took into consideration the air concentration, duration of exposure, and inhalation rate of the animal species studied (see **Appendix D** for calculations). This approach followed the dose calculation methods outlined in the 1992 U.S. EPA Exposure Assessment guidelines, where the potential dose is a function of the concentration and intake rate (U.S. EPA, 1992). It has generally been used for dietary exposure studies where the exposure concentration is expressed as the dose (for example, mg/kg/day) to account for consumption rate and duration of exposure. The doses indicated in the toxicology studies were not corrected for absorption. The critical NOELs used for risk characterization were adjusted with an 18% absorption factor since exposure estimates were expressed as absorbed doses (**IV.A.3. Critical NOELs and Reference Concentrations**).

[2] The required studies are: chronic toxicity (in two species), oncogenicity (in two species), reproductive toxicity (rats), developmental toxicity (in two species), genotoxicity, and neurotoxicity studies.

III.A. PHARMACOKINETICS

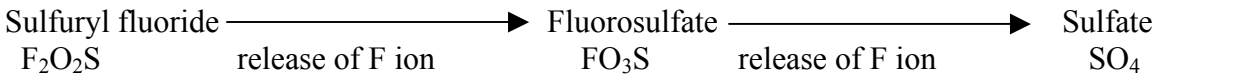
Fischer 344 male rats (4/dose with jugular vein cannulated, and 4/dose non-cannulated) received nose-only inhalation exposure (4 hours) to ^{35}S-sulfuryl fluoride at 30 and 300 ppm (Mendrala *et al*., 2002). Additionally, non-cannulated males (8/group) were exposed (4 hours, nose-only inhalation) to non-radiolabelled sulfuryl fluoride at 30 and 300 ppm and non-cannulated males (8) served as a vehicle control group, Time-weighted actual exposure concentrations with ^{35}S-sulfuryl fluoride were 28.4 ppm and 274 ppm at the 30 ppm and 300 ppm nominal levels respectively. Values were 31.2 ppm and 312 ppm, respectively, for non-radiolabelled sulfuryl fluoride exposures. The actual dose administered was unknown since the amount inhaled and inhalation rates of the rats were not determined. Using a default rat inhalation rate of 0.96 m^3/kg/day and a body weight of 0.2 kg (0.19 to 0.24 kg used in the study), the estimated doses given over the 4 hours were 37 *u*moles and 358 *u*moles, respectively, for 28.4 ppm and 274 ppm.[3] Blood, tissues (brain and kidney), and urine samples were collected and analyzed for radioactivity and fluoride levels at various times before, during, and after exposure.

No radioactivity was detected in expired air of the 300 ppm group animals at 24 hours post-exposure. Plasma levels of radioactivity peaked at 5.2 and 37.7 *u*g-equivalents/g (*u*g-eq./g) at 30 and 300 ppm respectively at the end of exposure. From the end of exposure to 24 hours post-exposure (alpha phase), half-lives were 2.6 and 2.4 hours at 30 and 300 ppm respectively, and from 24 hours post-exposure on (beta phase), half-lives were 82.7 and 56.2 respectively. Red blood cell radioactivity reached 4.7 and 40.3 *u*g-eq./g red blood cell at 30 and 300 ppm respectively at the end of exposure. The alpha phase half-lives were 2.5 and 1.1 hours and beta phase half-lives were 222 and 139 hours at 30 and 300 ppm respectively.

The lungs had the highest concentration of radioactivity, 0.77 and 6.30 *u*g-eq./g at 30 and 300 ppm respectively 7 days post-exposure. Respiratory turbinates contained 0.312 and 3.491 *u*g-eq./g, olfactory turbinates - 0.285 and 3.233 *u*g-eq./g, spleen - 0.394 and 3.075 *u*g-eq./g, and kidneys - 0.368 and 2.756 *u*g-eq./g at 30 and 300 ppm respectively. At 7 days post-exposure, the kidneys (0.368 *u*g-eq./g and 2.756 *u*g-eq./g), brain (0.227 *u*g-eq./g and 1.913 *u*g-eq./g), and spleen (0.394 *u*g-eq./g and 3.075 *u*g-eq./g) also contained relatively high levels of radioactivity. Detectable fluoride levels were found in the plasma, brain, and kidneys (Table 2).

After exposure, the majority of the radioactivity was detected in the urine (84% of absorbed) with lower levels in the feces (11% of absorbed) and tissues (5% of absorbed) (Table 2). Two radiolabelled metabolites, sulfate and fluorosulfate, as hydrolysis products, were identified in whole blood and urine. Elevated levels of fluoride ion were detected in urine, blood, plasma, kidney, and brain during and after exposure to sulfuryl fluoride (Table 2). Most fluoride levels returned to background levels at varying times post-exposure. The authors proposed the following metabolic scheme for sulfuryl fluoride, and that the rapid hydrolysis of sulfuryl fluoride supported the hypothesis that toxicity observed was due to fluoride, and not sulfuryl fluoride.

[3] 28.4 ppm x 4.17 mg/m^3 x 0.96 m^3/kg/day x 0.2 kg x day/24 hours x 4 hours x 1 mmole/102.07 mg =37 *u*mole



Based on the estimated dose of 37 *u*moles and 358 *u*moles for 30 ppm and 300 ppm, respectively, the total uptake was 18% and 16% (Table 2). Since human exposures are expected to be less than 30 ppm, the 18% value was used to calculate the absorbed doses in the exposure assessment for this document (DiPaolo and Beauvais, 2004; **Appendix A**).

Table 2. Distribution of ^{35}S-radioactivity and fluoride in the rat exposed to sulfuryl fluoride by inhalation.

Compartments	**30 ppm**			**300 ppm**		
^{35}S-sulfuryl fluoride levels as *u*mole-equivalent						
Compartments	Level	% absorbed	% dose	Level	% absorbed	% dose
Urine	5.69	85	15	45.24	82	13
Feces	0.71	10	2	7.61	14	2
Tissues	0.34	5	0.9	2.9	5	0.8
Total % estimated dose			18			16
Metabolite levels as *u*mole/ml						
Time	Sulfate	Fluorosulfate		Sulfate	Fluorosulfate	
Urine						
During exposure	0.15	0.44		2.34	8.24	
Post exposure 0 to 6 hrs	0.76	0.55		3.83	2.82	
6 to 12 hours	0.12	0.02		0.70	0.16	
12 to 24 hours	ND	ND		0.23	0.04	
Blood						
During exposure	9.7	27.3		50.3	118.7	
Post exposure 0 hour	21.0	34.4		62.2	134.5	
1 hour	9.0	19.5		32.4	74.8	
4 hour	ND	ND		18.7	4.5	
Fluoride levels as *u*mole fluoride/g						
Urine						
Non-exposed	0.117			0.134		
During exposure	0.491			4.013		
Post exposure 0 to 6 hrs	0.485			1.679		
6 to 12 hours	0.143			0.333		
12 to 24 hours	ND			0.265		
Plasma						
Non-exposed	0.033			0.033		
End of exposure	0.040*			0.132*		
Post exposure 2 hours	0.03			0.046		
4 hours	0.028*			0.037*		
8 hours	0.02*			00029*		
Brain						
Non-exposed	0.024			0.024		
End of exposure	0.042			0.119		
Post exposure 2 hours	0.041			0.070		
4 hours	0.042			0.052		
Kidney						
Non-exposed	0.119			0.119		
End of exposure	0.283*			0.292*		
Post exposure 2 hours	0.283			0.257		
4 hours	0.300*			0.265*		

a/ Data from Mendrala *et al*., 2002. For 30 ppm and 300 ppm, the respective total absorbed levels were 6.74 *u*mole-eq. and 55.75 *u*mole-eq, and the estimated total inhaled doses were 37 *u*moles and 358 *u*moles. ND=not determined. *= Significant difference from control at the indicated sacrifice time at $p<0.05$.

III.B. ACUTE TOXICITY

Summary: The lethal concentrations for 50% lethality (LC_{50}) in rats were 3020-3730 ppm for 1-hour exposure and 991-1500 ppm for 4-hour exposure. The 4-hour LC_{50} in mice was >400 ppm to 660 ppm. At non-lethal concentrations, neurotoxicity was observed in rats, mice, rabbits, and dogs. With acute to 2 weeks of exposures, clinical signs observed in these species included tremors, lethargy, respiratory effects, incapacitation, tetany, and convulsions. At the lowest-observed effect level, animals treated with sulfuryl fluoride for two weeks showed tissue damage in the kidney (rats), brain (rabbits, mice), and respiratory tract (rabbits and dogs). Available oral and dermal toxicity studies did not provide sufficient data for evaluation. A summary of effects from acute and 1-2 weeks of exposures is shown in Table 4.

III.B.1. Inhalation- Rat

In an acute neurotoxicity study of sulfuryl fluoride, non-pregnant female Fischer rats (12/group) were exposed to sulfuryl fluoride (purity 93.6-99.7%; 0, 100 or 300 ppm) by whole-body inhalation (6 hours/day) for 2 days (Albee *et al*., 1993a and b). Only females were used because they were more affected than males as measured by evoked potentials in a 13-week study (Mattsson *et al*., 1986). Mean measured concentrations were 0, 97 or 291 ppm. There was no treatment-related effect in Functional Observational Battery, grip performance, landing foot splay, motor activity and electrodiagnostic responses (flash evoked potential, auditory brainstem response to clicks, and somatosensory evoked potential) examined within 24 hours after the final exposure. The NOEL was 300 ppm (300 mg/kg/day), the highest dose tested. This study was considered supplemental information to DPR. U.S. EPA set a NOAEL of 300 ppm for lack of neurotoxicity and other effects at the highest dose tested (Hansen, 1993; U.S. EPA, 2004b).

In a 2-week study, Fischer 344 rats (5/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 100, 300, or 600 ppm) by whole-body inhalation for 6 hours per day and 5 days per week (Eisenbrandt *et al*., 1985; Eisenbrandt and Nitschke, 1989). The average measured concentrations were 0, 100, 293, and 597 ppm. At 600 ppm, 9/10 treated rats died or were moribund between the 2nd and the 6th dose. They were noted to be lethargic after the second exposure and "less active" with each additional exposure. Details on these observations were not provided in the report. Kidney effects (papillary necrosis, degeneration and regeneration of collecting tubules and proximal tubules) were noted in these animals with more severe findings in those that died early. At 300 ppm, 5/10 rats showed minimal renal changes (hyperplasia of the collecting ducts, basophilic epithelial cells in the proximal tubules) and statistically increased relative kidney weights in the female rats. Histopathological examinations showed no treatment-related effects in other organs including the brain and respiratory system. The acute NOEL was 300 ppm (300 mg/kg/day) for lethargy, morbidity and mortality at 600 ppm (600 mg/kg/day) after the second dose. The NOEL was 100 ppm (71 mg/kg/day) for kidney lesions at 300 ppm (214 mg/kg/day) after a two-week exposure.

Male rats (species not specified) were exposed to sulfuryl fluoride (purity not stated; 1000 to 15,000 ppm) by whole-body inhalation exposure for up to 6 hours (Dow Chemical Company, 1959). Measured concentrations were stated to be the same as the nominal concentrations. Treated rats showed tremors, convulsions, excess salivation, urination and

occasionally bloody tears during the exposure. Mortality was observed in all groups. After 2-3 hours of exposure, rats of the lowest dose (1000 ppm) were noted to show slight tremors and slight weight loss. There was one death (1/10 females) in this group after 2 hours of exposure. The estimated (from graphed data) 4-hour LC_{50} was 1500 ppm. The NOEL was <1000 ppm (<334 mg/kg/day) for tremors and death after 2-3 hours of exposure to 1000 ppm.

Fischer 344 rats (10/sex/group) were exposed to sulfuryl fluoride (purity 99.7%; 0, 250 to 2000 ppm) by whole-body inhalation for 4 hours and were observed twice daily for 14 days (Miller *et al*., 1980). Average measured concentrations were 450, 1000, 1250, 1425, or 2025 ppm for the male groups. They were 0, 320, 450, 700, 790, 1000, 1020, 1200, 1425, or 2025 ppm for the female groups. No effects were observed at 450 ppm or less after 4 hours of exposure. The 4-hr LC_{50}s were 1122 ppm and 991 ppm for males and females, respectively. At 1425 and 2025 ppm, treated rats showed sedation (20 minutes of exposure), prostration (40 minutes), convulsions (1-2 hours), and all died after 4 hours of exposure. At 1000-1250 ppm, some animals did not eat or drink and were lethargic, and some died. At or below 1000 ppm, no deaths occurred but some female animals in the "750" ppm group (the report did not specify whether it was the measured 700- or 790-ppm groups) showed lethargy. The body weight gain of the survivors was generally lower (some statistically significant at $p<0.05$) than that for the control during the 2-4 days after exposure. After 14 days, most of the animals recovered with only the 1000-ppm males showing significantly decreased body weight gain. There were no significant treatment-related effects on the organ weights of liver, kidney, brain, lung, and testes. Gross examination of the animals that died during exposure showed lesions primarily in the respiratory tract and included accumulation of secreted material near the nose and/or eyes, inflammation of the nasal cavity, and edema in the lungs. Histological examination was conducted only for the control, 1250-ppm males, and 1200-ppm females. Treatment related effects observed in animals killed or dead in these groups were: kidney (renal tubular degeneration 0/20 control *vs*. 7/20 treated for both genders), lung (mineralization and inflammation of the pleura 0/20 control *vs*. 1/20 treated), heart (multifocal myocardial degeneration 0/20 control *vs*. 1/20 treated) and spleen (cellular depletion of the red pulp or atrophy 0/20 control *vs*. 4/20 treated). No visible lesions were found in the brain. The acute NOEL was 450 ppm (300 mg/kg/day) for lethargy at 750 ppm (500 mg/kg/day) and mortality at 1000 ppm.

Male Fischer 344 rats (4/group) were exposed to sulfuryl fluoride (purity 99.8%; 0; 4,000; or 10,000 ppm) by head-only inhalation exposure for 20 minutes (Landry and Streeter, 1983). Measured concentrations were not given in the report, and the data were presented in graphical form. At 4,000 ppm, rats showed an initial increase in the mean respiratory frequency (maximum of 39%), but a decrease in mean tidal volume (maximum of 40%) and mean minute volume (maximum of 23%), when compared to pre-exposure levels. At 10,000 ppm, rats were more affected with a maximum of 60% increase in the mean respiratory frequency, maximum of 59% decrease in mean tidal volume, and maximum 53% decrease in mean minute volume, when compared to pre-exposure levels. These changes were transient as the maximum values for the group were measured after 1-2 minutes of exposure and were at near pre-exposure levels at 10 minutes of exposure and for the rest of the exposure duration. The 10,000-ppm rats were noted as "very ill" at the end of the 20-minute exposure but no clinical signs were specified. The authors considered these effects to be an indication of pulmonary irritation. The NOEL was

<4,000 ppm (<200 mg/kg/day) for respiratory effects at 4,000 ppm during the 20 minutes of exposure. This study was considered supplemental information to DPR.

Fischer 344 rats were exposed to 4,000 ppm (3 male/2 female) or 20,000 ppm (3 male/1 female) sulfuryl fluoride (purity 99.8%) by whole-body inhalation until death (Gorzinski and Streeter, 1985). Measured concentrations were not given in the report. The mean survival times were 79±10 minutes and 14±4 minutes for 4,000 ppm and 20,000 ppm, respectively. In the 4,000-ppm group, the body temperature decreased 7ºC over 80 minutes while the systolic blood pressure gradually increased from about 140 mm Hg to 185 mm Hg. The heart rate continued to decrease until death. Necropsy showed slight perivascular and alveolar edema. The NOEL was <4,000 ppm (<667 mg/kg/day) for effects on body temperature, blood pressure, and heart rate at 4,000 ppm. This study was considered supplemental information to DPR.

Male Fischer 344 rats (5/group) were exposed to sulfuryl fluoride (purity 99.8%; 4,000; 10,000; 20,000; 40,000 ppm) by whole-body inhalation and walked in a rotating motor-driven activity wheel at the same time (Albee *et al*., 1983; Nitschke *et al*., 1986). The protocol required that the animals walk for the first 10 minutes, then alternately rest for 2 minutes and walk for 1 minute for the next 9 minutes. Thereafter, still functioning animals rested for 5 minutes and walked for 1 minute until incapacitated. Measured concentrations were not given in the report. The times to incapacitation were: 41.5 minutes (4,000 ppm), 16.3 minutes (10,000 ppm), 10.3 minutes (20,000 ppm), and 6.4 minutes (40,000 ppm). Depending on the dose, the survival times were less than 10 minutes (20,000 and 40,000 ppm), 60 minutes (10,000 ppm), or 2.5 hours (4,000 ppm) after the end of exposure. Some rats showed tonic convulsions prior to death. Necropsy showed vascular congestion, pulmonary congestion, and alveolar and interstitial edema. Pretreatment of rats with calcium gluconate enhanced the survival of the 4,000-ppm group but had no effect on convulsions. Pretreatment of rats with an anticonvulsant (phenobarbital, diazepam, or diphenylhydantoin) prevented convulsions during sulfuryl fluoride exposure (Nitschke *et al*., 1986). As a post-exposure anticonvulsant for sulfuryl fluoride, phenobarbital was more effective than diazepam. Diphenylhydantoin, however, accentuated the toxicity of sulfuryl fluoride. The NOEL was <4000 ppm (<454 mg/kg/day) for incapacitation after 41 minutes of exposure. This study was considered supplemental information to DPR.

In a screening report of about 110 chemicals and solutions, rats (species not specified, 5/dose) were exposed to sulfuryl fluoride in bell jars or large desiccators for the determination of 1 hour lethal dose (Vernot *et al*., 1977). No details of the study were provided. The reported 1 hour LC_{50} were 3730 (3090-4510) ppm for males and 3020 (2830-3220) ppm for females.

III.B.2. Inhalation - Mouse

CD-1 mice (5/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 600, 700, or 800 ppm) by whole-body inhalation for 4 hours (Nitschke and Quast, 1990; Nitschke, 1994a). Mean measured concentrations were 0, 596, 692, or 806 ppm. No treatment-related effects were noted for mice in the 600-ppm group. There were deaths in the other groups: 9/10 for 700 ppm and 7/10 for 800 ppm. Body tremors and lethargy were observed in several mice in these two groups shortly after exposure. The reported LC_{50}s were 642 ppm and 660 ppm for males and

females, respectively. The acute NOEL was 600 ppm (751 mg/kg/day) based on tremors, lethargy, and death at 700 ppm (876 mg/kg/day) and 800 ppm. This study was considered acceptable with toxicity in Toxicity Category III under FIFRA guidelines.

B6C3F1 mice (5/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 400, 600, or 1000 ppm) by whole-body inhalation for 4 hours (Nitschke and Lomax, 1989). Mean measured concentrations were 0, 404, 603, or 1003 ppm. All mice at 600 ppm (5 days post exposure) and 1000 ppm (within 90 minutes) died. Some 600-ppm mice showed tremors and lethargy before death. No effects were observed for the 400-ppm group. The LC_{50} (male/female) was > 400 ppm (1.67 mg/L) but < 600 ppm (2.80 mg/L). The acute NOEL was 400 ppm (500 mg/kg/day) for tremor, lethargy, and death at 600 ppm (751 mg/kg/day). The study was considered acceptable with toxicity in Toxicity Category III under FIFRA guidelines.

CD-1 mice (5/sex/group) were exposed to sulfuryl fluoride (purity 99.6%: 0, 30, 100, and 300 ppm) by whole-body inhalation for 6 hours per day, 5 days per week, for 9 exposures (Nitschke and Quast, 2002). Mice were sacrificed 1 day after the last exposure and subjected to limited hematology and clinical chemistry studies, gross necropsy and histopathology. At 300 ppm, 9 of 10 mice died between day 7 and necropsy. Deaths were preceded by inanition (statistically significant body weight losses, decreased ingesta in digestive tract, decreased body fat), and associated pathology (stomach erosion/ulcers, hepatocellular atrophy). Most decedents had "roughened hair coat" and at least 3 of the males had whole body tremors. All high dose mice, except for 2 with tissue autolysis, showed cerebral vacuolation (7/8 moderate, 1/8 very slight). At 100 ppm, 4/5 males and 2/5 males showed very slight cerebral vacuolation. The high dose mice (4/5 males, 1/5 females) also had very slight vacuolation of the medulla. Also, nine high dose mice had lacrimal/Harderian gland atrophy. The NOEL was 30 ppm (40 mg/kg/day) based on cerebral vacuolation at 100 ppm (134 mg/kg/day). This study was considered acceptable to DPR under FIFRA guidelines.

III.B.3. Inhalation – Rabbit

New Zealand white rabbits (3/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 100, 300, or 600 ppm) by whole-body inhalation for 6 hours per day and 5 days per week for two weeks (Eisenbrandt *et al*., 1985; Eisenbrandt and Nitschke, 1989). The average measured concentrations were 0, 100, 293, and 597 ppm. One 600-ppm female rabbit had convulsions following the fifth exposure (Table 3). Another female rabbit had fractured vertebrum after the 6th dose but the cause was unknown as no convulsions were noted. Both rabbits were euthanized. Other rabbits were noted to be "slightly hyperactive" (time of onset and frequency were not given in the report). All rabbits in the 300-ppm and 600-ppm groups showed lesions in the cerebrum (Table 3). Vacuolation was found in the globus pallidus and putamen (basal nuclei) as well as the external and internal capsules (myelinated tracts). The cerebrum of all rabbits in the 600-ppm group and 2/6 of the 300-ppm group showed malacia[4] with reactive

[4] Malacia is defined as liquefaction necrosis (Quast *et al*., 1993c). The severity of very slight involves minimal localized amount of the caudate nucleus evaluated in the multiple sections. Slight indicates a larger size of the focal malacia involving 5 to 10% of the caudate nucleus. Moderate reflects greater than 10% of the section affected.

gliosis and demyelination. Tissue inflammation in the nasal, trachea, and bronchi/bronchioles was observed in the 300 ppm and 600 ppm rabbits. The NOEL was 100 ppm (40 mg/kg/day) for brain and respiratory tract lesions at 300 ppm (121 mg/kg/day). The U.S. EPA established a NOAEL of 100 ppm for focal malacia and vacuolation in the cerebrum and inflammation of the nasal tissue and trachea (U.S. EPA, 2004b; MRID 148956).

Table 3. Effects of sulfuryl fluoride in rabbits after 2-week inhalation exposure.[a]

Effects	**Males**				**Females**			
ppm	**0**	**100**	**300**	**600**	**0**	**100**	**300**	**600**
mg/kg/day	*0*	*40*	*121*	*241*	*0*	*40*	*121*	*241*
Clinical Observation								
Convulsion	0/3	0/3	0/3	0/3	0/3	0/3	0/3	1/3[b]
Hyperactivity- slight	0/3	0/3	0/3	3/3*	0/3	0/3	0/3	1/3
Histopathological Examination								
Cerebrum								
Malacia, bilateral, focal								
slight	0/3	0/3	0/3	0/3	0/3	0/3	1/3	2/3
moderate	0/3	0/3	1/3	3/3*	0/3	0/3	0/3	1/3
Vacuolation, bilateral,								
focal very slight	0/3	0/3	0/3	0/3	0/3	0/3	0/3	2/3
slight	0/3	0/3	3/3*	3/3*	0/3	0/3	3/3*	1/3
Nasal tissue								
Inflammation, multifocal								
slight	2/3	1/3	0/3	0/3	3/3	3/3	1/3	0/3
moderate	0/3	0/3	3/3*	3/3*	0/3	0/3	1/3	3/3*

a/ Data from Eisenbrandt *et al*., 1985. *=Significance at $p<0.05$ by the Fisher's Exact Test.
b/ One rabbit was euthanized after found with fractured vertebrum.

III.B.4. Inhalation - Dog

Beagle dogs (1/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 0, 30, 100, or 300 ppm) by whole-body inhalation (6 hours/day) for nine exposures over two weeks (Nitschke and Quast, 1991). Average measured concentrations were 0, 28.9, 96.3, or 298.2 ppm. No treatment-related effects were observed in the 30-ppm and 100-ppm groups. The clinical signs observed were intermittent tremors and tetany in both 300-ppm dogs from day 5 onward. Specific time of occurrence was not reported. These effects were so severe that exposure was terminated after 5.5 hours on day 9. Dogs were reported to show normal appearance and behavior within 30 minutes after exposure. Histopathologic examination of the cerebral cortex, brain stem, cerebellum and medulla oblongata did not show any tissue damage. Nasal turbinates and trachea of 300-ppm dogs showed inflammation and was considered slight. The NOEL was 100 ppm (29 mg/kg/day) based on clinical signs after 5 exposures and nasal tissue inflammation after two-weeks at 300 ppm (87 mg/kg/day).

III.B.5. Oral - Rat and Guinea Pig

In an overview, Quast (1988) summarized several acute studies but no details were provided. In the oral toxicity studies, rats (males and females) and guinea pigs (females) were

given sulfuryl fluoride bubbled into 1% corn oil. The LD_{50} was reported to be 100 mg/kg. In another study, rats were fed sulfuryl fluoride fumigated feed for 66 days. No treatment-related effects were noted in rats given feed fumigated with 2 lbs sulfuryl fluoride/1000 cubic feet of feed. However, dental fluorosis and kidney damage (not specified) were observed in animals treated at 10, 100, or 200 lbs sulfuryl fluoride/1000 cubic feet. The authors considered these findings to be consistent with those observed in inhalation toxicity studies.

III.B.6. Dermal - Rabbit

Quast (1988) also described a study with rabbits exposed to sulfuryl fluoride dermally for a total of 7 hours. A bag filled with sulfuryl fluoride was wrapped around the body but the report did not indicate any skin preparation or actual exposure concentration. No effects were reported.

Table 4. Acute and 1-2 week inhalation toxicity of sulfuryl fluoride.[a]

Species/ duration	Lethal Concentrations (LC_{50})- assigned as Category I by U.S. EPA	Ref.
Rat	4 hours: 1500 ppm	1
	1 hour: 3730 ppm (male), 3020 ppm (female)	2
	4 hour: 1122 ppm (male), 991 ppm (female)	3
Mouse	4 hour: 642 ppm (male), 660 ppm (female)	4*,5
	4 hours < 600 ppm (LC_{50}) > 400 ppm	6

Species/duration	NOEL/LOEL (ppm)	NOEL/LOEL (mg/kg/day)[b]	Effects at the LOEL	Ref.
Acute exposures (1-2 days)				
Rat 6 hr/d x 2d	**300 (HDT)/-**	**300 / >300**	**No effects (FOB, electrodiagnostic tests)**	**7**
Rat up to 6 hr	<1000 /1000	<334 / 334	Slight tremors after 2-3 hours of exposure and weight loss, 1 death	1
Rat 4 hr	450 / 750	300 / 500	Lethargy (females) at 750 ppm (mortality at 1000 ppm, tissue lesions at 1200-1250 ppm)	3
Rat 20 min (head-only)	<4000 / 4000	<200 / 200	Transient ↑ respiratory frequency, ↓ mean tidal volume & mean minute volume	8
Rat 1 hr	<4000 / 4000	<667 / 667	↓ Body temperature, ↑ blood pressure, ↓ heart rate, death	9
Rat 41 min	<4000 / 4000	<454 / 454	Incapacitation	10
Rat 6 hr/dx5d/w	300 / 600	300 / 600	Moribund and death between 2nd and 6th dose	11
Mouse 4 hr	600 / 700	751 / 876	Tremors, lethargy, death	4*
Mouse 4 hr	400 / 600	500 / 751	Tremors, lethargy, death	6*
1-2 weeks of exposure				
Rat 6 hr/d x 5d/w x 2w	100 / 300	71 / 214	Kidney lesions	11
Rat 6 hr/d x gd 6-15[b]	100 / 300	100 / 300	↓ Body weight; liver, kidney effects	12
Rat 6 hr/d x gd 6-15[b]	> 225 (HDT)	> 225	No effects observed	13*
Mouse 6 hr/d x5d/w x2w	30 / 100	40 / 134	Cerebral vacuolation	14*
Rabbit 6 hr/d x 5d/w x2w	**100 / 300**	**40 / 121**	**Brain & respiratory tract lesions; convulsion (after the 6th dose) & hyperactivity at 600 ppm**	**11**
Rabbit 6 hr/d x gd 6-18[c]	100 / 300	56 / 169	Maternal: ↓ body weight, ↓ liver weight	12
Rabbit 6 hr/d x gd 6-18[c]	75 / 225	42 / 127	Maternal: ↓ body weight	13*
Dog 6 hr/d x 5d/w x 2 w	100 / 300	29 / 87	Intermittent tremors and tetany (day 5 onward), nasal tissue inflammation (slight)	15

a/ Unless noted, all studies were conducted with whole-body exposures. Abbreviations: min=minutes, hr=hour, d=day, w=week, gd=gestation day, HDT=highest dose tested. * Indicates study acceptable to DPR under FIFRA guidelines. References: 1. Dow Chemical Company, 1959; 2. Vernot *et al*., 1977; 3. Miller *et al*., 1980; 4. Nitschke and Quast, 1990; 5. Nitschke, 1994a; 6. Nitschke and Lomax, 1989; 7. Albee *et al*., 1993a; 8. Landry and Streeter, 1983; 9. Gorzinski and Streeter, 1985; 10. Albee *et al*., 1983; 11 Eisenbrandt *et al*., 1985; 12. Hanley *et al*., 1980; 13. Hanley *et al.*, 1981; 14. Nitschke and Quast, 2002; 15. Nitschke and Quast, 1991. Bolded study is used for risk characterization.

b/ Equations for calculations are in **Appendix D**.

c/ Studies described under **III.G. DEVELOPMENTAL TOXICITY**.

III.C. SUBCHRONIC TOXICITY

Summary: After 13 weeks of inhalation exposure, the brain was the primary target for sulfuryl fluoride toxicity in all species studied (rats, mice, rabbits, and dogs). The most common lesion was vacuoles in the cerebrum. Other effects reported were nasal tissue inflammation (rats and rabbits), kidney hyperplasia (rats), lung histiocytosis (rats), thyroid hypertrophy (mice), and fluorosis (rats). A summary of the subchronic toxicity studies is presented in Table 10.

III.C.1. Inhalation - Rat

Fischer 344 rats (10/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 30, 100 or 300 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke *et al*., 1987a; Eisenbrandt and Nitschke, 1989). Average measured concentrations were 0, 29.8, 100 or 297 ppm. No clinical signs were observed. Mottled incisors were observed in all treated animals at 100 and 300 ppm. At 300 ppm, the body weights were reduced ($p<0.05$) after 24 and 45 days, for females and males respectively, of exposure. At termination (day 87), the body weights were 83% (males) and 85% (females), respectively, of controls. Pathological examination of the 300-ppm tissues showed slight cerebral vacuolation, kidney hyperplasia and decreased protein droplets, pulmonary subpleural histiocytosis and nasal mucosal inflammation (Table 5). The vacuolation was limited to the caudate-putamen nuclei. Special stains on the tissues did not provide any information on the characteristics of the vacuoles. The NOEL was 30 ppm (21 mg/kg/day) for mottled incisors at 100 ppm (71 mg/kg/day) and 300 ppm. For other effects, the NOEL was 100 ppm (71 mg/kg/day) for reduced body weights and histological changes in the brain, kidneys, lungs and nasal tissues at 300 ppm (214 mg/kg/day). This study was considered acceptable to DPR. U.S. EPA established only a NOAEL of 30 ppm for fluorosis.

Table 5. Histopathologic observations in rats after inhalation exposure to sulfuryl fluoride for 13 weeks.[a]

Effects	**Males**				**Females**			
ppm *mg/kg/day*	**0** *0*	**30** *21*	**100** *71*	**300** *214*	**0** *0*	**30** *21*	**100** *71*	**300** *214*
	Number of animals affected/Total in group							
Brain								
Vacuolation, cerebrum, focal: slight	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	10/10*
Kidney								
Hyperplasia, collecting ducts: very	0/10	0/10	0/10	0/10	0/10	0/10	0/10	9/10*
slight	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	0/10
↓protein droplets, cortex-very slight								
Lungs								
Alveolar histiocytosis, subpleural, slight	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	10/10*
Nasal Tissues								
Inflammation, mucosa diffuse:								
very slight/slight	0/10	0/10	0/10	7/10*	0/10	1/10	0/10	10/10*
moderate/severe	0/10	0/10	0/10	3/10	0/10	0/10	0/10	0/10

a/ Data from Nitschke *et al*., 1987a. *=Significance at $p<0.05$ by Fisher's Exact Test.

Fischer 344 rats (7/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 30, 100 or 300 ppm) by inhalation (6 hours/day, 5 days/week) for 13 weeks (Mattsson *et al*., 1986). A recovery group (2/sex/group at 0 or 300 ppm) was also treated and evaluated 2 months after exposure. Average measured concentrations were 0, 30, 100, and 297 ppm. Rats were implanted with epidural electrodes to monitor visual evoked response (FEP), cortical flicker fusion (CFF), auditory brainstem responses (ABR), cerebellar evoked response, somatosensory evoked response (SER-C and SER-S), and caudal nerve action potential. They were also subjected to a battery of neurological tests: hindlimb grip strength and an observation battery after the last exposure; but no treatment-related effects were observed at any dose. FEP and SER-S evoked responses were noted as significantly ($p<0.05$) slower in females at 100 ppm, and the ARB latency in the 100-ppm males appeared to be increased (Table 6). At 300 ppm, rats for both genders showed increased latencies of various evoked responses and decreased rates for CFF. The brain of all rats in this group showed vacuoles (mild) in the caudate-putamen nuclei (Table 6). Other pathological changes included inflammation of the nasal tissues and kidney changes (hyperplasia of collecting ducts, decrease in protein droplets in cortical tubules). The 300-ppm recovery group showed the normal auditory brainstem response and no brain vacuoles; these results suggested that the effects observed after the treatment was reversible. The NOEL was 30 ppm (21 mg/kg/day) based on changes in the electrophysiological tests at 100 ppm (71 mg/kg/day) and brain lesions at 300 ppm. In the published article, the authors reported mottled incisors, likely due to fluorosis, in all rats at 100 and 300 ppm with a NOEL of 30 ppm (21 mg/kg/day). This study was considered supplemental information to DPR. The U.S. EPA also established 30 ppm as the NOAEL for the study based on neurotoxicity, lung histopathology, and dental fluorosis (U.S. EPA, 2004b; MRID 40839902).

Table 6. Effects of sulfuryl fluoride in rats exposed to sulfuryl fluoride for 13 weeks and 2 months post-exposure.[a]

Duration	**Males**				**Females**			
ppm	**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
mg/kg/day	*0*	*21*	*71*	*214*	*0*	*21*	*71*	*214*
Electrophysiological responses (mean values for the group)								
FEP latency (msec)	-0.18	-2.05	-2.38	5.91*	0.00	0.05	11.87*	10.90*
CFF (flashes/sec)	45.26	48.33	46.86	42.67*	47.71	48.57	45.14	42.67*
ABR latency (msec)	0.02	0.04	0.14	0.18*	0.00	0.04	-0.03	0.16*
SER-C latency (msec)	-0.54	0.67	1.20	2.75*	0.51	0.86	-1.11	4.05*
SER-S latency (msec)	-0.36	-0.65	0.60	3.90*	0.17	2.56	4.44*	5.19*
Vacuoles in the cerebrum (Affected/Total examined)								
13-wk	0/3	0/6	0/7	4/4*	0/5	0/7	0/7	5/5*
2-month post-exposure	0/2	NA	NA	0/2	0/2	NA	NA	0/2

a/ Data from Mattsson *et al*., 1986. FEP=flash evoked response (visual), CFF=cortical flicker fusion (flash rate that elicits a synchronized cortical response), ABR=auditory brainstem response, SER-C=somatosensory evoked response in cortex, SER-S=somatosensory evoked response in cerebellum, and NA=dose groups not included in post-exposure phase of the study. *=Significance at $p<0.05$ by the Fisher's Exact Test.

III.C.2. Inhalation – Mouse

CD-1 mice (14/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 0, 10, 30, or 100 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke and Quast, 1993; Nitschke, 1994b). Average measured concentrations were 0, 10, 30 or 100 ppm. Three mice died (one each in 0, 10, and 100 ppm) and were not considered treatment-related. No effects were observed at 10 or 30 ppm. At 100 ppm, there were reduced body weight gain (10%) as well as reduced absolute brain, heart, kidney (male only), and liver weights. No effects were noted in Functional Observational Battery and hematology. Clinical chemistry showed increased triglycerides and alkaline phosphatase levels (male only). Histological examination showed multifocal vacuoles in cerebrum in almost all animals in the 100-ppm group (Table 7). The one mouse without brain vacuoles had died on day 63 of the study. In this group, there were also microvacuoles in the thalmus/hypothalamus region as well as very slight hypertrophy of follicular epithelial cells and decrease in colloid in thyroid gland. The NOEL was 30 ppm (40 mg/kg/day) based on brain and thalamus/hypothalamus vacuolation, and thyroid changes at 100 ppm (134 mg/kg/day). This study was considered acceptable to DPR.

Table 7. Incidences of vacuolation in the mouse brain exposed to sulfuryl fluoride for 13 weeks.[a]

Effects	**Males**				**Females**			
ppm	**0**	**10**	**30**	**100**	**0**	**10**	**30**	**100**
mg/kg/day	*0*	*13*	*40*	*134*	*0*	*13*	*40*	*134*
Cerebrum								
vacuolation, caudate putamen v sl	0/10	0/10	0/10	7/10*	0/10	0/10	0/10	3/10
sl	0/10	0/10	0/10	2/10	0/10	0/10	0/10	5/10*
vacuolation, external capsule v sl	0/10	0/10	0/10	7/10*	0/10	0/10	0/10	6/10*
sl	0/10	0/10	0/10	2/10	0/10	0/10	0/10	4/10*
Thalamus/hypothalamus								
vacuolation, external capsule v sl	0/10	0/10	0/10	9/10*	0/10	0/10	0/10	10/10*

a/ Data from Nitschke and Quast, 1993. v=very, sl=slight. Incidences indicated are affected/total in groups examined. *=Significance at $p<0.05$ by Fisher's Exact Test.

III.C.3. Inhalation - Rabbit

New Zealand white rabbits (7/sex/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 30, 100, or 600/300 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke *et al*., 1987b; Eisenbrandt and Nitschke, 1989). The highest dose group was initially exposed to 600 ppm but was reduced to 300 ppm after 9 exposures because two animals had convulsions. Average measured concentrations were 0, 29.8, 100, or 337 ppm. No treatment-related effects were observed at 30 ppm. At 300 ppm, there was a statistically significant ($p < 0.05$) decrement in body weight gain (about 10%) from day 11 to day 60 and in liver weight (ca. 26%). Nasal and brain lesions were observed in the 100 and 300-ppm groups (Table 8). At 100 ppm, vacuolation was observed in the cerebrum (internal and external capsules, putamen, and globus pallidus) of one female, and nasal inflammation in one male. While there was only a single incidence of brain vacuoles, this finding is of toxicological significance since the severity is moderate and there was increased in incidences at the next higher dose. At 300 ppm, brain and nasal tissue lesions were found in more animals and increased severity. The brain lesions included cerebral vacuolation, severe malacia, and gliosis as well as hypertrophy of vascular endothelial cells. Nasal tissues showed moderate to severe degeneration, inflammation, and hyperplasia/hypertrophy. The NOEL was 30 ppm (12 mg/kg/day) for brain and nasal lesions at 100 ppm (40 mg/kg/day) and 300 ppm. This study was considered acceptable to DPR. The U.S. EPA established a NOAEL of 30 ppm for the noted effects (U.S. EPA, 2004c; MRID 40890901).

Table 8. Histopathologic observations in rabbits after inhalation exposure to sulfuryl fluoride for 13 weeks.[a]

Effects	**Males**				**Females**			
ppm	**0**	**30**	**100**	**300[b]**	**0**	**30**	**100**	**300[b]**
mg/kg/day	*0*	*12*	*40*	*120*	*0*	*12*	*40*	*120*
	Number of animals affected/Total in group							
Brain Vacuolation, cerebrum, focal:								
very slight/slight	0/7	0/7	0/7	3/7	0/7	0/7	0/7	5/7*
moderate	0/7	0/7	0/7	0/7	0/7	0/7	1/7	0/7
Malacia, cerebrum, focal: severe	0/7	0/7	0/7	3/7	0/7	0/7	0/7	1/7
Gliosis, cerebrum, focal: slight	0/7	0/7	0/7	0/7	0/7	0/7	0/7	2/7
Hypertrophy, endothelium: very slight	0/7	0/7	0/7	0/7	0/7	0/7	0/7	2/7
Nasal Tissues								
Epithelial Degeneration, multifocal: slight	0/7	0/7	0/7	1/7	0/7	0/7	0/7	2/7
diffuse: slight/moderate	0/7	0/7	0/7	1/7	0/7	0/7	0/7	1/7
Submucosal inflammation,								
diffuse: severe	0/7	0/7	0/7	2/7	0/7	0/7	0/7	0/7
multifocal: very slight/slight	0/7	0/7	1/7	0/7	0/7	0/7	0/7	2/7
moderate	0/7	0/7	0/7	2/7	0/7	0/7	0/7	0/7
Epithelial hyperplasia/hypertrophy, diffuse:								
very slight/slight	0/7	0/7	0/7	3/7	0/7	0/7	0/7	3/7
moderate/severe	0/7	0/7	0/7	4/7*	0/7	0/7	0/7	3/7

a/ Data from Nitschke *et al*., 1987b. *=Significance at $p<0.05$ by Fisher's Exact Test. This group was exposed to 600 ppm for 9 exposures, the exposure level was reduced to 300 ppm for the rest of the experiment.

III.C.4. Inhalation - Dog

Beagle dogs (4/sex/group) were exposed to sulfuryl fluoride (purity 96.25%; 0, 30, 100, or 200 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 13 weeks (Nitschke and Quast, 1992). Average measured concentrations were 0, 29.9, 99.0, or 197.6 ppm. There were no effects at 30 and 100 ppm. In the 200-ppm group, there were decreased body weights of 88% and 96%, males and females, respectively, of control values by the end of the study ($p<0.05$ for both genders combined) (Table 9). Clinical signs were noted in one 200-ppm male and only on day 19 of the study. The observed signs were lateral recumbency, tetany, tremors, salivation, and incoordination. Histopathological examination of the mid-brain showed gliosis and vacuolation of focal areas of the putamen in one male and one female at 200 ppm. The NOEL was 100 ppm (29 mg/kg/day) based on reduced body weight gain and brain lesions at 200 ppm (58 mg/kg/day). The U.S. EPA established the NOAEL at the same dose as DPR (U.S. EPA, 2004b).

Table 9. Effects of sulfuryl fluoride in the cerebrum of dogs exposed to sulfuryl fluoride for 13 weeks.[a]

Effects	**Males**				**Females**			
ppm *mg/kg/day*	**0** *0*	**30** *9*	**100** *29*	**200** *58*	**0** *0*	**30** *9*	**100** *29*	**200** *58*
Mean body weight, grams, at end of study	13680	13522	12584	12095	11186	11882	11621	10757
% of control[b]	100%	99%	92%	88%*	100%	106%	104%	96%*
Clinical signs (affected/total in group)	0/4	0/4	0/4	1/4[c]	0/4	0/4	0/4	0/4
Histopathology (Affected[c]/Total examined)								
Gliosis, bilateral, focal, very slight	0/4	0/4	0/4	1/4	0/4	0/4	0/4	1/4
Vacuolation, bilateral, focal, very slight	0/4	0/4	0/4	1/4	0/4	0/4	0/4	1/4

a/ Data from Nitschke and Quast, 1992.

b/ Body weights for both gender were combined for statistical analysis (*=Significance at $p<0.05$ by the Fisher's Exact Test) since there were too few animals in each group.

c/ Clinical signs were observed only on day 19 and included: lateral recumbency, tetany, tremors, salivation, and incoordination.

d/ Gliosis and vacuolation were found in the same animal.

Table 10. Subchronic inhalation toxicity of sulfuryl fluoride.[a]

Species/ Exposure duration	NOEL/LOEL (ppm)	NOEL/LOEL (mg/kg/day)[b]	Effects	Ref.
Rat 6 hr/d x 5 d/w x 13 w	30 / 100 100/ 300	21 / 71 71 /214	Mottled incisors Reduced body weight and effects in brain (vacuoles, 20/20), kidney (hyperplasia), lungs (alveolar histiocytosis) and nasal (inflammation) tissues	1*
Rat 6 hr/d x 5 d/w x 13 w	30 / 100 30 / 100	21 / 71 21 / 71	Mottled incisors Electrophysiological effects (brain lesions at 300 ppm and incidence of 9/9)	2
Mouse 6 hr/d x 5 d/w x 13 w	30 / 100	40 /134	Brain (9-10/10) and thalamus/hypothalamus vacuoles, thyroid hypertrophy	3*
Rabbit 6 hr/d x 5 d/w x 13 w	**30 / 100**	**12 / 40**	**Brain (vacuoles) and nasal (inflammation) lesions**	**4***
Dog 6 hr/d x 5 d/w x 13 w	100/ 200	29 / 58	Reduced body weight gain, brain lesion (gliosis and vacuoles, 2/8)	5

a/ Abbreviations: hr=hour, d=day, w=week. * Study was acceptable to DPR under FIFRA guidelines. References: 1. Nitschke *et al*., 1987a; 2. Mattsson *et al*., 1986; 3. Nitschke and Quast, 1993; 4. Nitschke *et al*., 1987b; 5. Nitschke and Quast, 1992. Bolded study is used as the critical study for risk characterization. Incidences for brain lesions were noted in parentheses.

b/ Equations for calculations are in **Appendix D**.

III.D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: After chronic exposure, the primary target tissue for sulfuryl fluoride was the brain and the respiratory tract in rats, mice, and dogs. As with subchronic exposure, brain vacuoles were observed in the cerebrum. The lesions in the respiratory tract included nasal tissues, trachea, larynx, and lungs. Dental fluorosis was observed in both rats and dogs. Progressive glomerulonephropathy was considered the cause of death in sulfuryl fluoride treated rats. Sulfuryl fluoride was not oncogenic in rats, mice, and dogs. A summary of the chronic toxicity studies is presented in Table 14.

III.D.1. Inhalation - Rat

In the satellite group of a chronic toxicity study, Fischer 344 rats (15/sex/group) were exposed to sulfuryl fluoride (93.6-99.7% purity; 0, 5, 20, or 80 ppm) by whole-body inhalation exposure (6 hours/day, 5 days/week) for 1 year (Spencer *et al*., 1994). This study was designed only to evaluate the neurotoxicity of sulfuryl fluoride and was part of a 2-year study (Quast *et al.*, 1993a). Measured concentrations were not reported. No treatment-related effects were observed in Functional Observational Battery, grip performance, landing foot splay and motor activity test. The NOEL for neurotoxicity was $ 80 ppm ($57 mg/kg/day). This study was considered supplemental information to DPR.

Fischer 344 rats (50/sex/group) were exposed to sulfuryl fluoride (99.8% purity; 0, 5, 20, or 80 ppm) for 24 months (6 hours/day, 5 days/week, except holidays) (Quast *et al*., 1993a). The average measured concentrations were 0, 5.1, 20.2, or 79.6 ppm. There was increased mortality in the 80-ppm groups. By the end of the study, the mortality rates were 100% (the last animal died between day 701-707) for treated males and females, compared with 42% (males) and 50% (females) for control. Decreased body weights were noted for the 80-ppm males (86% of control) and all treated female groups (84% of control for 80 ppm) (Table 11). Premature death in this group was caused by chronic progressive glomerulonephropathy and mineralization/ atrophy in a variety of tissues (aorta, bone, eyes, heart, liver, mammary gland, mediastinal tissues, mesenteric tissues, parathyroid glands, pituitary glands, spleen, stomach, and tongue). Glomerulo-nephropathy (very slight or slight), was noted in all groups including the control with the highest incidence in the 20-ppm females (Table 11). At the next dose, the severity of glomerulo-nephropathy progressed to moderate and severe level. Mineralization/atrophy in tissues either did not appear or reach an advanced degree until well beyond the first year of the study, and were considered being secondary to renal toxicity. Clinical chemistry showed significant ($p<0.05$) changes (male/females in % of control) in the 80-ppm groups and included: elevated blood urea nitrogen (488%/555%), creatinine (400%/371%), phosphorus (207%/231%), and cholesterol levels (244%/164%), and reduced blood albumin levels (77%/72%).

Very slight multifocal vacuolation in the cerebrum and thalamus/hypothalamus was observed only in the 80-ppm females (Table 11). The authors suggested that perivascular edema was the cause of the vacuolation, which surrounded vessels in the dorsolateral outer cortical region. This vacuolation was considered not related to those observed in other studies because of the difference in affected location (caudate putamen region identified in other studies) and only females were affected. The authors also suggested that it might be associated with the “advanced

chronic renal disease for females". However, glomerulonephropathy showed only a gender difference at 20 ppm but similar incidences at 80 ppm for both genders.

Possible direct responses of respiratory tissues to sulfuryl fluoride included aggregates of alveolar macrophages in lungs, and inflammation of larynx and trachea (Table 11). Dental fluorosis, graded as slight or very slight, in the males and females was observed at 20 ppm (16 mg/kg/day) and 80 ppm, respectively, with a NOEL of 5 ppm (4 mg/kg/day) for males (Table 11). The NOEL for non-dental effects was 20 ppm (14 mg/kg/day) based on kidney, brain and respiratory tract lesions at 80 ppm (57 mg/kg/day). There was no evidence of oncogenicity. This study was considered acceptable to DPR. The U.S. EPA established a NOAEL of 5 ppm for fluorosis at 20 ppm in male rats and a NOEL of 20 ppm for tissue effects (effects in the kidneys, adrenal cortex, brain, eyes, liver, nasal tissues, respiratory tract) at 80 ppm for female rats (Hansen, 1998; U.S. EPA, 2004b; MRID 43216702). The NOAEL for neurotoxicity was 80 ppm, the highest dose tested.

Table 11. Effects of sulfuryl fluoride in rats after inhalation exposure for 2 years.[a]

Effects	**Males**				**Females**			
ppm	**0**	**5**	**20**	**80**	**0**	**5**	**20**	**80**
mg/kg/day	*0*	*4*	*14*	*57*	*0*	*4*	*14*	*57*
Body weights (g and % of control)								
Day 565	436	427 (98%)	428 (98%)	374* (86%)	259	240* (93%)	250* (96%)	218* (84%)
Day 734	402	389 (97%)	379 (94%)	NA	255	265 (104%)	258 (101%)	NA
Histopathology (Affected/Total examined)								
Dental Fluorosis	0/50	0/50	10/50*	50/50**	0/50	0/50	2/50	50/50**
Glomerulonephropathy								
very slight/slight	21/50	25/50	25/50	2/50*	47/50	47/50	50/50	3/50*
moderate/severe	28/50	22/50	24/50	5/50*	0/50	0/50	0/50	7/50*
very severe	1/50	2/50	1/50	43/50*	1/50	0/50	0/50	40/50*
Brain vacuoles								
Cerebral cortex	2/50	0/50	1/50	1/50	1/50	3/50	3/50	22/50*
Thalmus/hypothalamus	2/50	0/50	1/50	1/50	1/50	3/50	2/50	22/50*
Larynx- Inflammation								
acute	6/49	2/49	5/49	11/49	3/49	0/49	1/49	18/49*
chronic	6/49	6/49	7/49	18/49*	0/49	1/49	1/49	0/49
Lungs- Aggregates of alveolar macrophages								
very slight/slight	4/50	1/50	2/50	15/50*	2/50	0/50	3/50	6/50
moderate	1/50	0/50	0/50	34/50*	0/50	0/50	0/50	42/50*
Nasal tissues								
Reactive hyperplasia	3/50	2/50	2/50	31/50*	4/50	1/50	2/50	26/50*
Inflammation	12/50	7/50	8/50	33/50*	22/50	20/50	17/50	32/50*
Trachea Inflammation	1/50	0/50	0/50	9/50*	1/50	0/50	0/50	1/50

a/ Data from Quast *et al*., 1993a. Significantly different from control, *p <0.05 or **p<0.01, using either the Dunnett's or Wilcoxon's tests from the report. NA=all animals died between day 701 and 707.

III.D.2. Inhalation - Mouse

CD-1 mice (50/sex/group) were exposed to sulfuryl fluoride (99.8% purity; 0, 5, 20, or 80 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 18 months (Quast *et al*., 1993b). Satellite groups (10/sex/group) were sacrificed at 12 months. Average measured concentrations were 0, 5.1, 20.1, or 79.7 ppm. There were no treatment-related effects in the satellite groups or in the 5 and 20- ppm groups in the 18-month study. In the 80-ppm/18 month group, the body weights were consistently lower ($p<0.05$) than the control throughout the experiment (Table 12). By day 551, they were 85% (female) and 86% (male) of control values. In this group, there was increased mortality in females mainly due to increased incidence of systemic amyloidosis, noted by the investigators for CD-1 mice as having a genetic predisposition for this lesion (Table 12). By day 555, 64% (males) and 72% (females; $p<0.05$) of the 80-ppm group died compared to 46% (males) and 36% (females) in the controls. Other treatment-related effects included food impaction in the esophagus (12/50 males versus 3/50 in control) and inflammation and/or abscesses in the head and/or oral cavity at 80 ppm. Pathological examinations showed very slight vacuolation in both caudate putamen and external capsule of the cerebrum of 80-ppm groups at 12 months (Table 12). At 18 months, vacuolation was observed only in the external capsule with no increase in severity. The 80-ppm groups also showed increased incidences of thyroid epithelial cell hypertrophy (20/49 treated *vs.* 0/49 control males, $p<0.05$), heart thrombus (14/50 treated *vs.* 4/50 control females), and lung congestion (19/50 treated *vs.* 6/50 control females, $p<0.05$). The NOEL was 20 ppm (27 mg/kg/day) based on systemic amyloidosis, brain, thyroid, heart, and lung effects at 80 ppm (107 mg/kg/day). There was no evidence of oncogenicity. This study was considered acceptable to DPR. The U.S. EPA also determined a NOAEL of 20 ppm (20 mg/kg/day)[5] with a LOAEL of 80 ppm for decreased survival, body weight gain, and tissue effects (Hansen, 1998; U.S. EPA, 2004b; MRID 43354903).

Table 12. Effects of sulfuryl fluoride in mice after inhalation exposure for 18 months.[a]

Effects	**Male**				**Female**			
ppm *mg/kg/day*	**0** *0*	**5** *7*	**20** *27*	**80** *107*	**0** *0*	**5** *7*	**20** *27*	**80** *107*
Body weight on day 551 (mean, g; % control)	41.0	41.6 (101%)	40.8 (100%)	35.3 (86%)	34.9	34.1 (98%)	35.0 (100%)	29.8 (85%)
Mortality (# mice dead)	23/50	20/50	25/50	25/50	18/50	12/50	20/50	36/50*
Systemic amyloidosis[b]	11/50	12/50	15/50	10/50	6/50	5/50	13/50	26/50*
Brain, vacuoles, v. slight caudate putamen 12 months	0/10	0/10	0/10	1/10	0/10	0/10	0/10	0/10
external capsule								
12 months	0/10	0/10	0/10	10/10*	0/10	0/10	0/10	9/10*
18 months	0/50	0/50	0/50	13/50*	0/50	0/50	0/50	12/50*

a/ Data from Quast *et al*., 1993b. * =Significance at $p<0.05$. v.=very

b/ Affected /total animals in the group. Affected = those died with amyloidosis as cause of death.

[5] 20 ppm x 4.17 x 0.01m^3/6 hrs x 1/0.03 kg x 5/7=19.84 mg/kg/day.

III.D.3. Inhalation - Dog

Beagle dogs (4/sex/group) were exposed to sulfuryl fluoride (99.8% purity; 0, 20, 80, or 200 ppm) by whole-body inhalation (6 hours/day, 5 days/week) for 1 year (Quast *et al*., 1993c). Average measured concentrations were 0, 21, 79 or 198 ppm. The 200-ppm group was sacrificed at 9 months due to severe toxicity (breathing difficulties, decreased activity, and pale skin and mucous membranes). This group also had lower weight gain than the control within the first two weeks of exposure (Table 13). By day 278, the females lost 526 grams, compared to gains of 1462 grams for the males and 3100 grams for the controls. Body weights of other treated groups were not affected. At 80 ppm, there were chronic active inflammation in the lung alveoli, multifocal aggregates of alveolar macrophages, and dental fluorosis (Table 13). At 200 ppm, the incidence and severity were increased for those effects (except for alveolar macrophages). The malacia was considered slight/moderate and involved only the head of the caudate nucleus. Neuropil and macrophages were found within the malacia foci but normal appearing cells were adjacent to the foci. The authors suggested ischemic tissue damage as the cause of the malacia. Additional effects in the thyroid (hypertrophy), lymph node (atrophy), thymus (atrophy), tonsil (atrophy), and liver (atrophy) were found in this group. The NOEL was 20 ppm (6 mg/kg/day) based on dental fluorosis and lung lesions at 80 ppm (23 mg/kg/day). There was no evidence of oncogenicity. This study was considered acceptable to DPR. U.S. EPA selected a NOAEL of 20 ppm with a LOEL of 80 ppm for decreased body weight gain, lung histopathological changes, and dental effects (Hansen, 1998; U.S. EPA, 2004b; MRID 43354901).

Table 13. Effects of sulfuryl fluoride in dogs after inhalation exposure for 9-12 months.[a]

Effects	**Male**				**Female**			
ppm *mg/kg/day*	**0** *0*	**20** *6*	**80** *23*	**200** *58*	**0** *0*	**20** *6*	**80** *23*	**200** *58*
Mean Body Weight Gain (g)								
12 days	493	587	602	201	367	268	465	284
278 days	3184	4554	3225	1462	3175	2875	2788	-526*
Tissue Effects- (Affected/ Total examined)								
Lungs-inflammation								
very slight	0/4	0/4	0/4	2/4	0/4	0/4	2/4	1/4
moderate/severe	0/4	0/4	0/4	2/4	0/4	0/4	0/4	3/4
Alveolar macrophages aggregates	0/4	0/4	3/4	0/4	0/4	0/4	1/4	0/4
Brain-malacia, caudate nucleus								
very slight, slight	0/4	0/4	0/4	2/4	0/4	0/4	0/4	2/4
moderate	0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4
Tooth- fluorosis-								
very slight, slight	0/4	0/4	3/4	4/4*	0/4	0/4	1/4	4/4*

a/ Data from Quast *et al*., 1993c. The 200-ppm group was exposed to sulfuryl fluoride for only 9 months. M=males, F=females. *=Significance at $p<0.05$ by Fisher's Exact Test.

Table 14. Chronic inhalation toxicity of sulfuryl fluoride.

Species/ Exposure duration	NOEL/LOEL (ppm)	NOEL/LOEL (mg/kg/day)[b]	Effects	Ref[a]
Rat 6 hr/d x 5 d/w x 1 y	>80 /-	>60 /-	No neurotoxicity	1
Rat 6 hr/d x 5 d/w x 2 y	5 / 20 20 / 80	4 / 14 14 / 57	Dental fluorosis (males) Brain vacuoles, glomerulonephropathy, and respiratory tract macrophages and inflammation (females)	2*
Rat **6 hr/d x 5 d/w x 2-generation study[c]**	**5 / 20** 20/150 20 / 150	**4 / 14** 14 /107 14 /107	**Maternal- lung inflammation and alveolar macrophage aggregates** Maternal-brain vacuoles Reproductive- reduced pup body weight	**3***
Mouse 6 hr/d x 5 d/w x 2 y	20 / 80	27 /107	Decreased body weight, decreased survival, systemic amyloidosis, brain vacuoles, thyroid hypertrophy, heart thrombus, and lung congestion	4*
Dog 6 hr/d x 5 d/w x 1 y	20 / 80 20 / 80 80/ 200	6 / 23 6 / 23 23 / 58	Dental fluorosis Lung inflammation and alveolar macrophage aggregates Brain malacia	5*

a/ Abbreviations: hr=hour, d=day, w=week, and y=year. *Study was considered acceptable to DPR according to FIFRA guidelines. References: 1. Spencer *et al*., 1994; 2. Quast *et al*., 1993a; 3. Breslin *et al*., 1992; 4. Quast *et al*., 1993b; 5. Quast *et al*., 1993c. Bolded study is used as the critical study for risk characterization.

b/ Equations for calculations are in **Appendix D**.

c/ Study described in **III.F. REPRODUCTIVE TOXICITY**. The exposure was 5 days/week during premating, but 7 days/week during gestation and lactation.

III.E. GENOTOXICITY

Summary: Sulfuryl fluoride was not genotoxic in either *in vitro* or *in vivo* studies.

III.E.1. Gene Mutation

Salmonella typhimurium strains (TA1535, TA1537, TA98 and TA100) were exposed to sulfuryl fluoride (purity 99.6%; 0; 300; 1,000; 3,000; 10,000 and 30,000 ppm) for 4 hours with and without rat liver S9 fraction (Gollapudi *et al*., 1990a). After exposure, the plates were incubated for 2 days before the colonies were counted. There was no increase in the reversion rate. The number of revertants was actually lower at 30,000 ppm than that for the control. For example, the mean revertants/plate without S9 were 16 for control and 10 for the 30,000-ppm group. This study was considered acceptable to DPR. U.S. EPA also concluded that there were no significant treatment-related effects in this study (U.S. EPA, 2004b; MRID 41603001).

III.E.2. Structural Chromosomal Effects

CD-1 mice (15/sex/group) were exposed to sulfuryl fluoride (purity 99.6%; 0, 50, 175, or 520 ppm) by whole-body inhalation for 4 hours (Gollapudi *et al*., 1990b; Nitschke and Gollapudi, 1991). Average measured concentrations were 0, 48, 180, or 520 ppm. Bone marrow samples from the femurs were examined at 24, 48, or 72 hours after exposure. There was no increase in the number of micronucleated cells. No clinical signs were reported. This study was considered acceptable to DPR. U.S. EPA also concluded that there were no significant treatment-related effects in these studies (U.S. EPA, 2004b; MRID 41769102, 41448601).

III.E.3. Other Genotoxic Effects

Isolated hepatocytes from rats (Sprague-Dawley outbred Crl:CD BR male) were plated in tubes and exposed to sulfuryl fluoride (purity 97.4%; 0, 204, 408, 612, 816, 1020, or 1530 ppm) (Gollapudi *et al*., 1991). While the period of treatment was 18-19 hours, cells in the tubes were rocked so that half of them were exposed to sulfuryl fluoride in the air at a time. There was no induction of unscheduled DNA synthesis as measured by autoradiography. This study was considered acceptable to DPR. U.S. EPA also concluded that there was no increase in unscheduled DNA synthesis in this study (U.S. EPA, 2004b; MRID 42179802).

III.F. REPRODUCTIVE TOXICITY

Sprague-Dawley rats (30/sex/group) were exposed to sulfuryl fluoride (purity 97.32%; 0, 5, 20, or 150 ppm) by inhalation (6 hours/day) in a 2-generation study (Breslin *et al*., 1992; Kirk *et al*., 1992). The rats were exposed for 5 days/week during premating (for 10 weeks for F0 and 12 weeks for F1, excluding holidays); and 7 days/week during mating (1 to 3 weeks), gestation (3 weeks), and lactation (3 weeks). The females were not exposed to sulfuryl fluoride from gestation day 21 to postpartum day 4 (about 10 days). The pups (F1 generation) from F0 parents were exposed *in utero* during gestation and via the maternal milk from birth to postnatal day 21, but no direct exposure until premating at about 6 weeks old. The average measured concentrations during F0 and F1 generations were 0, 5.0, 20.9 and 149.1 ppm, and 0, 5.2, 20.4, and 150.1 ppm, respectively. For the calculation of daily dosages, DPR calculated dosages were based on the longer continuous period, which was during premating at 5 days per week. This approach also took into consideration the days of no exposure during the periods of 7 days per week of exposure. The daily dosages were: 0, 4, 14, and 107 mg/kg/day, respectively, for 0, 5, 20, and 150 ppm.

No parental effects were noted at 5 ppm. At 150 ppm, adults of both generations had body weight decrements of about 10%. These reductions were generally statistically significant at $p<0.05$ during various measured periods. The teeth of these groups also showed various treatment-related effects (discoloration of lower incisors, overgrown incisors, broken upper incisors, malformation) (Table 15). At > 5 ppm, there were increased incidences of pathological findings in the lung and brain for both generations (Table 15). At 20 ppm and 150 ppm, the lungs showed increased incidences of aggregates of alveolar macrophages as multiple, round, pale, or gray loci. The aggregates were most commonly found in the subpleural or peribronchial locations. At 150 ppm, there were also increased incidences of chronic inflammation in the lungs. The incidences for moderate severity for these endpoints were higher in the F1 parents than those in the F0 parents. The authors of the report considered these indications of lung injury. In comparison, the incidences for brain vacuolation at the 150 ppm group were higher in the F0 than F1 parents. The severity was described as “very slight to slight” vacuolation of myelinated fiber tracts in the cerebrum.

The only effect on the pups was reduced body weight. F1 litter body weights were significantly reduced from day 1 (female only) to day 21 of lactation (Table 15). By day 21, they were 84% of control values. For the F2 litters, the reduction in body weight was also observed during lactation; however, the female pup weight reduction was statistically significant only on day 14 and 21. The parental systemic NOEL was 5 ppm (4 mg/kg/day) based on lesions in the lung at 20 ppm (14 mg/kg/day). The reproductive NOEL was 20 ppm (14 mg/kg/day) for reduced pup body weight in F1 and F2 generations at 150 ppm (107 mg/kg/day). This study was considered acceptable to DPR. The U.S. EPA established the NOAELs for the following endpoints: 5 ppm for parental toxicity (pathological changes in the lung), 150 ppm for reproductive toxicity (no effect at the highest dose tested), and 20 ppm for offspring toxicity (decreased pup body weight) (U.S. EPA, 2004b; MRID 42179801).

Table 15. Effects of sulfuryl fluoride in adult rats and pups in a 2-generation reproductive toxicity study.[a]

Effects **ppm** *mg/kg/day*	**0** *0*	**5** *4*	**20** *14*	**150** *107*
Gross pathology (Affected in both genders/Total examined)				
F0 parents				
Lungs-focus, gray, multifocal	0/60	0/60	5/60*	48/60*
Oral tissues- effects on incisors[b]	1/60	2/60	2/60	56/60*
F1 parents				
Lungs-focus, pale	1/60	0/60	10/60*	36/60*
Oral tissues- dark tooth	0/60	0/60	0/60	42/60*
Histopathology[c] (Affected in both genders/Total examined)				
F0 parents				
Alveolar macrophage aggregates				
very slight to slight	10/60	15/59	30/60*	40/60*
moderate	0/60	0/59	0/60	20/60*
Lungs-chronic inflammation				
very slight to slight	4/60	5/59	2/60	39/60*
Brain vacuolation, cerebrum, bilateral				
very slight to slight	0/60	0/59	0/59	25/60*
F1 parents				
Alveolar macrophage aggregates				
very slight to slight	24/60	23/60	38/60*	36/60*
moderate	0/60	0/60	2/60	23/60*
Lungs-chronic inflammation				
very slight to slight	3/60	4/60	4/60	23/60*
moderate	0/60	0/60	0/60	2/60
Brain vacuolation, cerebrum, bilateral				
very slight to slight	0/60	0/60	0/60	9/60*
Pup body weight (mean, grams; % control)				
F1 litters				
day 1 M	7.2	7.1 (99%)	7.2 (100%)	7.0 (97%)
F	7.1	6.6 (93%)	6.7 (94%)	6.6* (93%)
day 21 M	42.6	40.7 (96%)	43.0 (101%)	35.6* (84%)
F	41.4	38.1 (92%)	41.0 (99%)	34.7* (84%)
F2 litters				
day 1 M	6.8	7.0 (103%)	7.2 (106%)	6.7 (99%)
F	6.4	6.6 (103%)	6.8 (106%)	6.2 (97%)
day 21 M	41.5	43.8 (106%)	42.9 (103%)	38.3 (92%)
F	39.8	42.4 (107%)	41.7 (105%)	35.6* (89%)

a/ Data from Breslin *et al*., (1992). Thirty animals in each group were examined except 29 for histopathology of the 20 ppm F0 male group. *=Significance at $p<0.05$ by Fisher's Exact Test.

b/ Incisor effects include: dark, lower incisors; overgrown incisors; worn, broken upper incisors, and malformation, upper incisors. Some animals have more than one effect.

c/ Severity for alveolar macrophage aggregates: very slight=1 to 3 small aggregates, slight=3 to 6, usually larger aggregates, and moderate=> 6 large aggregates.

III.G. DEVELOPMENTAL TOXICITY

Summary: There were no teratogenic effects in rats or rabbits exposed to sulfuryl fluoride during gestation. The only fetal effect observed was reduced fetal body weight in rabbits, but not in rats. Maternal toxicity was limited to reduced body weights.

III.G.1. Inhalation - Rat

In a range-finding study, pregnant Fischer 344 rats (10/group) were exposed to sulfuryl fluoride (purity not stated; 0, 30, 100, or 300 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 15 (Hanley *et al*., 1980). The number of pregnant rats per group was 7, 8, 9, or 9 for 0, 30, 100, or 300 ppm. The respective average measured concentrations were 0, 30, 101, or 299 ppm. The 300-ppm dams showed a significant ($p<0.05$) decrease in body weight (day 16, 92% of control), body weight gain (day 6-15, gain of 3.3 g compared to 24.6 g for control), and food consumption (73-79% of control throughout the study); increase in water consumption (168 to 212% of control throughout the study) and absolute (107% of control), and increase in relative (118% of control) kidney weights. Gross pathological examination showed effects in the liver (diffuse paleness from equivocal to moderate, 7/9), kidney (subcapsular paleness in foci or areas, 8/9), and intestine (decreased contents, 2/9). There was no histological examination of the brain. No effects on the fetus were observed. The NOEL for maternal toxicity was 100 ppm (100 mg/kg/day) for effects on body weight, kidney weight, food consumption and water consumption at 300 ppm (300 mg/kg/day).

Pregnant Fischer 344 rats (35-36/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 25, 75, and 225 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 15 (Hanley *et al*., 1981 and 1989). The average measured concentrations were 0, 25, 76, or 225 ppm. There was neither maternal toxicity nor developmental toxicity. There was no histological examination of the brain. The maternal and developmental NOELs were > 225 ppm (>225 mg/kg/day). This study was considered acceptable to DPR. The U.S. EPA established 225 ppm (the highest dose tested) as the NOAEL for maternal and developmental toxicity (U.S. EPA, 2004b; MRID 00090015).

III.G.2. Inhalation - Rabbit

In a range-finding study, pregnant New Zealand white rabbits (7/group) were exposed to sulfuryl fluoride (purity not stated; 0, 30, 100, or 300 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 18 (Hanley *et al*., 1980). The number of pregnant rabbits per group was 7, 6, 5, or 7 for 0, 30, 100, or 300 ppm. The respective average measured concentrations were 0, 30, 101, or 299 ppm. The 300-ppm does showed significant ($p<0.05$) decreases in body weight (day 19, 87% of control), body weight gain (day 6-18, loss of 408.8 g compared to gain of 7.9 g in control), and absolute (65% of control) and relative (74% of control) liver weights. Gross pathological examination showed slight pale accentuation of the lobular pattern of the liver in 4 of 7 rabbits in the 300-ppm group. There was no histological examination of the brain. No effects on the fetus were observed. The maternal NOEL was 100 ppm (56 mg/kg/day) for body weight and liver weight effects at 300 ppm (169 mg/kg/day).

Pregnant New Zealand rabbits (28-29/group) were exposed to sulfuryl fluoride (purity 99.8%; 0, 25, 75, or 225 ppm) by whole-body inhalation (6 hours/day) on gestation day 6 to 18 (Hanley *et al.*, 1981 and 1989). The average measured concentrations were 0, 25, 76, or 225 ppm. The significant ($p<0.05$) effects observed were reduced (loss of 60 g compared to a gain of 240 g in control) overall maternal body weight gain and fetal body weight (86% of control) in the 225-ppm group. There was no histological examination of the brain. The maternal and fetal NOEL was 75 ppm (42 mg/kg/day) for reduced body weights at 225 ppm (127 mg/kg/day). This study was considered acceptable to DPR. The U.S. EPA established the NOAEL of 75 ppm for both maternal toxicity (decreased body weight and body weight gain) and developmental toxicity (decreased fetal body weight) (U.S. EPA, 2004b; MRID 00090015).

III.H. NEUROTOXICITY

Under FIFRA guidelines, a delayed neurotoxicity study is not required for sulfuryl fluoride. Acute neurotoxicity effects were described under **III.B. ACUTE TOXICITY**.

III.I. HUMAN EXPOSURE

III.I.1. Non-occupational Exposure

In the first case report, a man was exposed to both sulfuryl fluoride and chloropicrin for 4 hours with "limited ventilation" (Taxay, 1966). The initial symptoms were nausea, vomiting, crampy abdominal pain, and pruritus. Physical examination at the hospital showed reddened conjunctiva, pharyngeal and nasal mucosa; diffuse rhonchi; and paresthesia of the right leg. He was discharged 4 days later. The serum fluoride concentration was noted only as positive. The sulfuryl fluoride air concentration was not measured at the time of exposure but was reported to be 5 ppm "several hours" after the incident.

In a report of three cases, individuals were exposed to high concentrations of sulfuryl fluoride (Scheuerman, 1985). The first case involved a man who entered a tarped and fumigated apartment before aeration. Postmortem examination of this man showed congestion in the mucosa of the larynx, trachea, bronchi, and lungs. The fluoride concentration was 50.42 mg/L, measured 24 to 36 hours postmortem. In the second case, a man was found dead next to an opened sulfuryl fluoride gas container. The postmortem examination showed congested respiratory and lung mucosa, and edematous brain tissues. In the third case, a woman was exposed to sulfuryl fluoride after entering a fumigated home not cleared for reentry. Her initial symptoms were coughing, chest discomfort, and hypotension. Approximately 6 hours after exposure, she showed hyperexcitability, hyperventilation, and tachycardia. She eventually died after developing severe pulmonary edema, carpal/pedal tetany, cardiac and dysrhythmias. The antemortem fluoride concentration was 20 mg/L.

An elderly couple was exposed to sulfuryl fluoride in their house cleared for reentry (Dammann *et al*., 1987). While the fumigation company opened windows and doors, and aerated

the house with fans, sulfuryl fluoride level was not measured. It was not detected when the air was analyzed 12 days after aeration. The couple experienced weakness, nausea and shortness of breath that evening. The man suffered a seizure and died the following day. His wife's condition got worse with pulmonary edema and died after a cardiovascular arrest 6 days later. Her serum fluoride level was 0.5 mg/L, 4 days after the exposure. For this case, the "expected" background fluoride level was reported to be 0.01 mg/L.

III.I.2. Occupational Exposure

Fumigators using methyl bromide and sulfuryl fluoride in California were evaluated using neurobehavioral tests (Anger *et al*., 1986). The workers were divided into four groups: reference (29 workers on jobs related to the fumigation but were not exposed to fumigants), sulfuryl fluoride (24 workers who use sulfuryl fluoride 80% of the time), methyl bromide (32 workers who use methyl bromide 80% of the time), and combination (18 workers who use both fumigants 40-60% of the time). The number of days since last fumigation ranged from "hours" to 14-15 days for sulfuryl fluoride and combination groups, and ranged from "hours" to 61 days for the methyl bromide group. The methyl bromide group reported a higher prevalence of muscle aching and fatigue, and increased threshold for the two-point test for finger sensitivity, and a lower number of facts recalled in the Wechsler Memory Scale. This group also consistently showed lower performances on neurobehavioral test measures. Mild neurologic dysfunctions were observed in some subjects; they included increased tremors, unsteadiness on standing with eyes closed, ataxia, and poor grip strength. For the sulfuryl fluoride group, there was an increased prevalence of general symptoms and reduced performance on cognitive tests. The authors offered the following caveats for the results: (1) lack of information on participation rates and bias; (2) group differences in age, educational level, race, alcohol consumption, use of prescription drugs, and use of "illegal drug"; and (3) the possibility of over-reporting of symptoms.

In a cross-sectional study of 123 structural fumigation workers in Florida, the majority (112) was exposed to methyl bromide (MB) and sulfuryl fluoride, with the remaining workers exposed to sulfuryl fluoride only (Calvert *et al*., 1998). The medians of years worked with MB and sulfuryl fluoride were 1.2 years (range 0-22.1 years) and 2.85 years (0.11 to 20.5 years), respectively. Neurological function tests included: nerve conduction, vibration testing, neurobehavioral tests (hand-eye coordination, simple reaction time, continuous performance test, symbol digit test, pattern memory for cognitive and visual memory, serial digit learning, mood scales), vocabulary test, Santa Ana Dexterity test, postural sway testing, contrast sensitivity (visual), olfactory, and urine analysis. The only significant findings were reduced performance on the pattern memory test and reduced olfactory function for workers with high sulfuryl fluoride exposure (used sulfuryl fluoride on 50% or more of jobs).

Reduction of dexterity and median nerve functions, and the prevalence of carpal tunnel syndrome were attributed to repetitive stress from the use of heavy-duty spring clamps. The authors found few health effects associated with MB but noted that the study had limited power to assess the exposures. The potential biases and limitations included: use of friends and neighbors as controls, study design (e.g. temporal sequence of cause and effect, and use of

workers still in fumigation), and concomitant exposure (some workers were exposed to both MB and sulfuryl fluoride).

IV. RISK ASSESSMENT

IV.A. HAZARD IDENTIFICATION

The most appropriate data for the hazard identification are those from human studies. However, human case reports of sulfuryl fluoride exposure (**III.I. HUMAN EXPOSURE**) did not provide sufficient data for evaluation. In the absence of human data, results from animal studies were extrapolated to humans assuming that the effects observed in laboratory animals would also be observed in humans. Toxicity endpoints and critical NOELs for risk characterization are discussed in this section. Only those endpoints considered of toxicological significance were used for hazard identification.

IV.A.1. Selection of Endpoints

The primary target tissues for sulfuryl fluoride inhalation toxicity are the brain, respiratory system, and teeth. While dental fluorosis could be attributed to fluoride, the mechanism of toxicity for the other endpoints is unknown. The registrant has proposed that fluoride was the causative agent for all toxic effects observed in sulfuryl fluoride treated animals (Dow AgroSciences, 2004). This was based only on the results of the pharmacokinetic study where only two metabolites (fluoride and fluorosulfate) were detected (Mendrala *et al*., 2002). Of these, fluoride was considered the toxicant of concern. This position needs more supportive data. Published studies showed that fluoride can bind with cations such as calcium, potassium, and magnesium (Scheurmann, 1985) but the relationship between this activity and system effects has not been established. Studies with fluoride have not shown to cause brain vacuolation or respiratory effects. Furthermore, the absence of fluorosis in mice after subchronic (Nitschke *et al*., 1987a) and chronic (Quast *et al*., 1993b) suggested that brain lesions could occur in the absence of fluoride.

IV.A.1.a. Neurotoxicity – Brain Vacuolation and Malacia

In humans, the effect of sulfuryl fluoride on the nervous system is unclear. There are indications of potential neurotoxicity as described in the DPR's Pesticide Illness Surveillance Program reports (**II.E. ILLNESS REPORTS**) or case reports (**III.I. HUMAN EXPOSURE**). However, these reports do not provide sufficient information to establish a cause-effect relationship. In addition, some workers were known to be exposed to other chemicals, in particular methyl bromide, a known neurotoxicant and a fumigant (Anger *et al*., 1986; Calvert *et al*., 1998).

There is sufficient evidence for neurotoxicity in experimental animals. Clinical signs included tremors, lethargy, convulsion, hyperactivity, and incoordination (Table 4). The most prominent pathological lesion is the vacuolation and/or malacia of the cerebrum in all species (rats, mice, rabbits, and dogs) tested (Table 16). Both lesions were described as focal in nature and were found in the caudate putamen nucleus, the external capsule and internal capsule, and/or the globus pallidus. In all studies where the brain was examined, the incidence and severity of the vacuolation was dose-related (Table 3, 5-9, 11-13, and 15). The incidences at the low and

mid-doses generally involved none or few animals but involved disproportionately more animals at the high dose. At increasing concentration, the severity progressed only from very slight to slight in most studies, but to moderate in few studies.

The brain lesions also were related to the duration of exposure with the LOEL at lower doses with longer exposure duration (Table 16). For rats, rabbits, and mice, the LOELs for 2-week or 13-weeks of exposure were higher than those for chronic studies. For example in rats, the LOELs were 214 mg/kg/day for vacuolation in two 13-week studies (Nitschke *et al*., 1987a and Mattsson *et al*., 1986) and 107 mg/kg/day in the chronic study (Breslin *et al.*, 1992). Similarly, the LOELs were 134 mg/kg/day for the 13-week study (Nitschke and Quast, 1993) and 107 mg/kg/day for 18 months in the mouse chronic toxicity study (Quast *et al*., 1993b). The duration-effect relationship was less clear in dogs where the same dose (58 mg/kg/day) caused vacuolation and gliosis in the 2-week study (Nitschke and Quast, 1991), but malacia in the 1-year study (Quast *et al*., 1993c). Malacia could be considered a more severe effect.

The cause of the vacuolation and malacia in the brain after sulfuryl fluoride exposure is unknown. Vacuolation is a pathological term for a clear space (sphere) in the brain tissue; it may be part of the degenerative process such as that following ischemia (Gopinath *et al*., 1987). With sulfuryl fluoride, some investigators hypothesized that the vacuolation was due to perivascular edema (Quast *et al*., 1993a) and malacia was due to ischemic tissue damage (Quast *et al*., 1993c). The regionality of the lesions suggested sulfuryl fluoride affected regional metabolism (Eisenbrandt and Nitschke, 1989). The use of conventional and special stains[6] did not provide any indication of the cause of the lesions. Vacuolation in brain tissues has been observed with other pesticides. For example, chlorfenapyr, a pyrrole compound with insecticidal and miticidal activities, caused vacuolation in the mouse brain white matter after chronic exposure (U.S. EPA, 1999b). The finding was thought to be associated with the edema between the myelin layers. In a 2-week toxicity study, permethrin caused vacuolation and swelling of unmyelinated fibers and Schwann cell hypertrophy in rats (Glaister *et al*., 1977). In neural diseases, the formation of intracellular vacuoles in the brain is a marker for the diagnosis of a group of neural degenerative diseases called spongiform encephalopathies (De Girolami *et al*., 1999). Vacuolation of the neurons in the cerebrum, cerebellum, and other nuclei is also a finding in aging rats (Solleveld and Boorman, 1990).

[6] Stains used were: hematoxylin-eosin, luxol fast blue-periodic acid Schiff (lipids/myelin, glycogen), and Sevier-Munger (neural tissues) stains.

Table 16. The lowest-observed-effect levels (LOELs) for brain lesions and clinical signs in sulfuryl fluoride-treated animals.[a]

Duration/ Species (ref)		Clinical Signs		Brain Lesions	
		LOEL	Findings	LOEL	Findings
2-week	Rat (1)	600	Moribund		(Not conducted)
	Mouse (2)	402	Tremors	134	Vacuoles- very slight (6/10)
	Rabbit (1)	241	Convulsion, hyperactivity	121	Vacuoles-slight, 6/6 Malacia-moderate, 2/6
	Dog (3)	89	Tetany and tremors		(Not conducted)
13-week	Rat (4)	>200	No effect	214	Vacuoles-slight, 20/20
	Rat (5)	71	No effects in hindlimb grip strength and FOB but changes in evoked potential responses.	214	Vacuoles–severity not reported, 9/9
	Mouse (6)	>134	No effect on FOB	134	Vacuoles-very slight/slight, 17-19/20 in 3 regions
	Rabbit (7)	>120	No effect	40	Vacuoles-moderate, 1/14, malacia/ gliosis at next dose at 120 mg/kg/day
	Dog (8)	58	Clinical signs[b] (1/8) only on day 19	58	Vacuoles- very slight, 2/8, Gliosis- very slight, 2/8
Chronic	Rat (9)	> 57	No effect on FOB	57	Vacuoles[c] –very slight, 23/100
	Rat (10)	>107	No effect	107	Vacuoles- very slight/slight, 25/60 (F0), 9/60 (F1)
	Mouse (11)	>107	No effect	107	Vacuoles-very slight, 25/100
	Dog (12)	> 58	No effect	58	Malacia-very slight/moderate, 5/8

a/ References in parenthesis are: 1. Eisenbrandt *et al*., 1985; 2. Nitschke and Quast, 2002; 3. Nitschke and Quast, 1991; 4. Nitschke *et al*., 1987a; 5. Mattsson *et al*., 1986; 6. Nitschke and Quast, 1993; 7. Nitschke *et al*., 1987b; 8. Nitschke and Quast, 1992; 9. Quast *et al*., 1993a; 10. Breslin *et al*., 1992; 11. Quast *et al*., 1993b; 12. Quast *et al*., 1993c. FOB=functional observation battery.

b/ Signs included lateral recumbency, tetany, tremors, salivation, and incoordination.

c/ Not considered the same effect as in other studies.

With sulfuryl fluoride exposure, the vacuolation in the brain tissue did not appear to be related to clinical signs or electrophysiological changes in the brain. As shown in Table 16, most of the studies did not show the presence of clinical signs. In the few studies with reported clinical signs, the LOELs were higher than those for the brain lesions. Mattsson *et al* (1986) showed the vacuolation was not related to the changes in evoked potential responses after sulfuryl fluoride treatment. The LOEL for the evoked potential responses were also lower (71 mg/kg/day) than that for brain vacuolation (214 mg/kg/day) (Table 6). Furthermore, sulfuryl fluoride-treated rat brain tissues showed no vacuolation and normal evoked potentials 2 months after the last exposure (Mattsson *et al*., 1986). While these findings suggested the effects were reversible, the significance of this apparent reversibility was unclear. The interpretation of the result was limited since there were only two animals per group and only two groups (control and high dose) were studied.

Therefore, the findings of vacuolation and malacia were considered toxicologically significant as indicators of neurotoxicity. They were clearly related to sulfuryl fluoride treatment and were found in multiple animal species. The long-term and functional consequence of such damage and the mechanism of toxicity remained to be elucidated.

IV.A.1.b. Respiratory System Effects

The respiratory system was also a target for sulfuryl fluoride toxicity after inhalation exposure. DPR's Pesticide Illness Surveillance Program reported individuals complaining of respiratory problems after exposures to sulfuryl fluoride and chloropicrin (Mehler, 2001). It is not know if one or both contributed to the symptoms. Respiratory tract effects were also reported in humans after accidental or intentional acute exposures (**III.I.1. Non-occupational Exposure**). Postmortem examination findings in humans included respiratory and lung congestion, and pulmonary edema after exposure to high concentration during application (Scheurman, 1985) and lower concentration in a house cleared for reentry (Dammann *et al*., 1987).

In experimental animals, pharmacokinetic study in rats showed highest radioactivity in the lungs after inhalation exposure (Mendrala, 2002). At high concentrations during acute exposure, sulfuryl fluoride is a respiratory irritant resulting in increased respiratory frequency, and reduced mean tidal and minutes volumes in rats (Landry and Streeter, 1983). At lower concentrations and short exposure durations (2 to 13 weeks), there was inflammation of the larynx, nasal tissue, and trachea inflammation in rats (Nitschke *et al*., 1987a; Table 5), rabbits (Eisenbrandt *et al*., 1985; Nitschke *et al*., 1987b; Tables 3 and 8) and dogs (Nitschke and Quast, 1991). With chronic exposure, chronic inflammation (Quast *et al.*, 1993c; Breslin *et al*., 1992; Tables 13 and 15) and alveolar macrophage aggregates (Quast *et al*., 1993a; Quast *et al*., 1993c; Breslin *et al*., 1992; Tables 11, 13, and 15) were found in rats and dogs, and lung congestion was observed in mice (Quast *et al*., 1993b).

IV.A.1.c. Dental Fluorosis

In addition to neurotoxicity and respiratory effects, one prominent effect was fluorosis from repeated exposure to fluoride ion. Mottled tooth enamel or dental fluorosis was reported in rats and dogs after repeated sulfuryl fluoride exposures (Tables 11, 13, and 15). No dental effects were reported in mice after chronic exposure (Quast *et al*., 1993b) at dosages higher as those in the rat and dog chronic toxicity studies (Table 14). The U.S. EPA has stated that fluorosis was a cosmetic effect, and not an adverse effect (U.S. EPA, 2004b). The National Academy of Sciences is currently examining the issues related to the fluoride exposure and toxicity (see footnote 1). The toxicity of fluoride associated with sulfuryl fluoride uses and other sources will be addressed in the dietary risk assessment.

IV.A.2. Selection of No-Observed-Effect Levels

Critical NOELs were established for exposure durations: acute (1 day), 1-2 week, subchronic (13-weeks), and chronic exposures. These NOELs would be used to address the exposure scenarios of workers, bystanders, and residents described in **IV.B. EXPOSURE ASSESSMENT**.

IV.A.2.a. Acute Toxicity

For acute exposure, the critical NOEL was 300 mg/kg/day (300 ppm, the highest dose tested) for no effects in Functional Observational Battery or electrophysiological responses in rats after two days of exposure (Albee *et al*., 1993a). This NOEL was supported by the same NOEL of 300 mg/kg/day from two studies (Eisenbrandt *et al*., 1985; Miller *et al*., 1980) (Table 4). In these latter studies, treatment-related effects (lethargy at 500 mg/kg/day and death at 600 mg/kg/day, respectively) were observed at the next dose. In comparison, a head-only exposure study by Landry and Streeter (1983) showed a lower LOEL of 200 mg/kg/day (4000 ppm for 20 minutes) for respiratory effects. However, the estimated NOEL (ENEL) from this study was not selected because of the quality of the study and the transient nature of the effect. The results were available only as graphs and sulfuryl fluoride concentrations were relatively high with actual measurements not given in the report. The effects were transient with peak effect after 2 minutes of exposure and gradually returned to pre-exposure level by 10 minutes of post-exposure. They were likely indication of pulmonary irritation. This ENEL may be appropriate for accidental exposures to relatively high concentrations but not for the lower exposures associated with label-use of sulfuryl fluoride. Higher NOELs (500 and 751 mg/kg/day) were found for mice where tremors, lethargy, and death were observed when exposed to 751 and 876 mg/kg/day (600-700 ppm) sulfuryl fluoride in two 4-hour studies (Nitschke and Quast, 1990; Nitschke and Lomax, 1989). These results in mice and the finding of one death in the rat study between the 2nd and 6th dose (Eisenbrandt *et al*., 1985) at about 2-fold of the NOEL suggested a steep dose-response relationship for sulfuryl fluoride neurotoxicity.

IV.A.2.b. 1-2 weeks Exposure Toxicity

For exposures of 1-2 week in duration, the critical NOEL was 40 mg/kg/day (100 ppm) for malacia and vacuoles in the cerebrum of rabbits exposed to 121 mg/kg/day (300 ppm) sulfuryl fluoride (Tables 3 and 4) for two weeks (Eisenbrandt *et al*., 1985). The magnitude of the effect (and incidence) in rabbits at the LOEL were considered slight to moderate (2/6) for malacia and slight (6/6) for vacuolation. Neurotoxicity (convulsions after the 6th dose and slight hyperactivity) was observed at the higher dose of 600 ppm. This NOEL was supported by similar findings, though less severe, in mice with the same NOEL (Nitschke and Quast, 2002). In two developmental toxicity studies with rabbits at similar doses (NOELs of 56 mg/kg/day and 42 mg/kg/day) (Table 4), the only finding was reduced body weight at 169 and 127 mg/kg/day after the first week of exposure (Hanley *et al*., 1980 and 1981). However, it was not known if there were any brain lesions since histopathological examination was not conducted in the maternal tissues. External, soft tissue, and skeletal examination of the fetuses did not show any treatment-related effects in these studies.

In rats, no brain lesions were observed in the 1-2 week studies although the animals treated at 420 mg/kg/day (600 ppm) were either moribund or died early in the study (Eisenbrandt *et al*., 1985). In this group, the primary histopathological effect was in the kidneys (hyperplasia of the collecting ducts and basophilic epithelial cells in the proximal tubules) with the NOEL at 71 mg/kg/day (100 ppm). Kidney effects (focal paleness), along with reduced body weight and liver effects with a NOEL of 100 mg/kg/day (100 ppm), were observed in pregnant rats in a range-finding developmental toxicity study (Hanley *et al*., 1980). These effects, however, were not observed in the definitive developmental toxicity study (Hanley *et al*., 1981).

In dogs, a lower NOEL of 29 mg/kg/day (100 ppm), compared to 40 mg/kg/day for rabbits (Eisenbrandt *et al*., 1985), was determined for intermittent tremors and tetany on day 5 onward as well as nasal tissue inflammation at 87 mg/kg/day (300 ppm) (Nitschke and Quast, 1991). However, this study was not selected for the determination of the critical NOEL because of the quality of the study. The study had only one dog per group per gender. The specific times of occurrence and frequency for the tremors and tetany were not reported. While the effects were considered severe and the exposure was terminated on day 9, the dogs were also reported to show normal appearance and behavior within 30 minutes afterward. Lesions were not observed in the histological examination of the brain. Since the LOEL for clinical signs was at 87 mg/kg/day, the use of the NOEL of 40 mg/kg/day as the critical NOEL should be adequate to address these clinical observations in dogs.

As for the inflammation effect on the dog nasal tissue, the severity was graded as slight at the LOEL (300 mg/kg/day; Nitschke and Quast, 1991) with the actual NOEL likely to be closer to the LOEL. This effect has also been observed in rabbits at 121 mg/kg/day (300 ppm) after 2 weeks of exposure (Eisenbrandt *et al*., 1985; Table 3).

IV.A.2.c. Subchronic Toxicity

With subchronic inhalation exposure (13-weeks) to sulfuryl fluoride, brain vacuoles were observed in rats, mice, rabbits, and dogs (Table 10). The most sensitive species for this endpoint was the rabbit with the critical NOEL at 12 mg/kg/day (30 ppm) (Nitschke *et al*., 1987b). While the incidence was only 1/7 and affecting only females at the LOEL of 40 mg/kg/day (100 ppm), the lesion was considered toxicologically significant as it was graded moderate. In addition, a higher incidence of vacuolation and more severe lesions (malacia and gliosis) were observed at 300 ppm. The NOELs for brain effects were higher in other species. In rats, the NOELs were 71 mg/kg/day (100 ppm, Nitschke *et al*., 1987a; Table 5) and 21 mg/kg/day (30 ppm, Mattsson *et al*., 1986; Table 6). For mice and dogs, the NOELs were 40 mg/kg/day (30 ppm, Nitschke and Quast, 1993; Table 7) and 29 mg/kg/day (100 ppm, Nitschke and Quast, 1992; Table 9), respectively. The selection of 12 mg/kg/day (30 ppm) in rabbits for brain lesions as the critical NOEL would also protect against other effects such as nasal tissues, kidneys, lungs, and thyroid lesions as well as dental fluorosis with the same or higher NOELs (Table 10).

IV.A.2.d. Chronic Toxicity

With chronic exposure to sulfuryl fluoride, dental fluorosis and respiratory system effects were the more sensitive endpoints with lower NOELs than that for brain lesions (Table 14). The critical NOEL was 4 mg/kg/day (5 ppm) in rats for dental fluorosis in a chronic toxicity study (Quast *et al*., 1993a; Table 11) and for lung inflammation and alveolar macrophage aggregates in a 2-generation reproductive toxicity study (Breslin *et al*., 1992; Table 15). This critical NOEL was supported by a similar NOEL of 6 mg/kg/day (20 ppm) for similar pulmonary findings in dogs (Quast *et al*., 1993c; Table 13). In comparison, brain vacuolation was observed at higher doses (LOELs at ≥ 57 mg/kg/day and NOELs at ≥ 14 mg/kg/day) in these studies (Table 14). For the purpose of this risk assessment, respiratory system effects were considered the critical effect for chronic inhalation exposure of sulfuryl fluoride.

IV.A.2.e. Oncogenicity of Sulfuryl Fluoride

Sulfuryl fluoride was not oncogenic in chronic inhalation studies conducted using rats, mice, and dogs. Both DPR and U.S. EPA concluded that it was not genotoxic in *in vitro* and *in vivo* genotoxicity assays. U.S. EPA classified sulfuryl fluoride as a chemical “not likely to be carcinogenic to humans” (U.S. EPA, 2004b and c).

IV.A.3. Critical NOELs and Reference Concentrations

The critical NOELs and reference concentrations for risk characterization are presented in Table 17. The NOELs and LOELs were adjusted with an inhalation absorption factor of 18% (see **III.A. PHARMACOKINETICS**) since human exposures are expressed in absorbed dose terms (DiPaolo and Beauvais, 2004). The assumption is that the extent of absorption in rats was the same as that in humans. The reference concentrations, as 24-hour time weighted averages, were based on uncertainty factors of 100 (10-fold each for intraspecies and interspecies extrapolation) for occupational and of 1000 (with an additional 10-fold factor for the lack of a developmental neurotoxicity study) for residential/bystander exposures. The higher inhalation rate (lower reference concentration) of infants, compared to older children and adult groups, was used to calculate the reference concentrations for residents/bystanders as a group. In comparison, the maximal reference concentrations would be those for adults whose inhalation rate (0.28 m^3/kg/day) was about 2-times those for infants (0.51 m^3/kg/day used in **Appendix A**).

Table 17. Critical no-observed-effect levels (NOEL) and reference concentrations for the risk characterization of sulfuryl fluoride.

Duration	NOEL/ LOEL (ppm)	NOEL/ LOEL (mg/kg/day)	NOEL in absorbed dose[a] (mg/kg/day)	Reference concentration[b]		Critical Endpoint	Ref.[c]
				Workers (Adult) UF=100	Residents/ Bystanders (Infants) UF=1000		
Acute 1 day	300/>300	300/>300	54	2.57 ppm 10.72 mg/m^3	0.14 ppm 0.59 mg/m^3	No effect in FOB and electro-physiological tests in rats	1
1-2 weeks	100/300	40/121	7.2	0.48 ppm 2.01 mg/m^3	0.026 ppm 0.11 mg/m^3	Brain lesion (malacia and vacuoles) in rabbits	2
Sub-chronic (13-week)	30/100	12/ 40	2.2	0.14 ppm 0.60 mg/m^3	0.008 ppm 0.03 mg/m^3	Brain lesion (vacuoles) in rabbits	3*
Chronic	5/20	4/ 14	0.72	0.04 ppm 0.18 mg/m^3	0.002 ppm 0.01 mg/m^3	Lung inflammation, alveolar macrophage aggregate in rats	4*

a/ The absorbed dose was calculated using a 18% inhalation absorption factor.

b/ The reference concentration (RfC) as 24-hour time-weighted averages is the ratio of human equivalent NOEL (**Appendix D**) to a default uncertainty factor. When the UF is 1000, an additional 10x database factor was included. The RfC for occupational exposure was based on human adult inhalation rate of 0.28 m^3/kg/day, and for residential/bystander exposure was based on infant inhalation rate of 0.51 m^3/kg/day used in Appendix A.

c/ * indicates study acceptable to DPR under FIFRA guidelines. References: 1. Albee *et al*., 1993a; 2. Eisenbrandt *et al*., 1985; 3. Nitschke *et al*., 1987b; 4. Breslin *et al*., 1992.

IV.B. EXPOSURE ASSESSMENT

Workers, residents, and bystanders are exposed to sulfuryl fluoride from its use in structural and non-food commodity fumigations. Detailed discussion of the exposure assessment is in **Appendix A**. The inhalation exposure estimates were based either on monitoring studies or an assumed air level. They were expressed as absorbed doses using an inhalation absorption factor of 18% based on a pharmacokinetic study in rats. The exposure durations were defined as acute (24 hours or less), short-term (7 days or less), intermediate (more than 7 days to less than 1 year), annual (any exposure during the year), and lifetime (Andrews, 2001). Some of these durations were different than those defined by the U.S. EPA[7] (U.S. EPA, 2001b).

IV.B.1. Occupational Exposure

Occupational exposures for fumigators and tent crews were based on personal air monitoring data. For handlers of non-food commodity fumigation, their exposures were assumed at 5 ppm, the maximum exposure limit according to the current Vikane® label.

IV.B.1.a. Structural Fumigation - Fumigators and Tent Crew

For structural fumigation, exposures were estimated for fumigators during phases of the application and aeration, and tent crew workers doing detarping activities (Table 18). The frequency of exposure per activity was 0.17 to 3.73 hours per day, about 4 days per week, and for 180 or 196 days per year depending on the activity. For the individual activities, the short-term exposures for the fumigators were calculated using the 95th percentile air concentrations from personal air monitoring studies of workers using submaximal application rate of sulfuryl fluoride. Their exposures ranged from 0.000006 mg/kg/day (closing of structure) to 0.029 mg/kg/day (introducing fumigant) (Table 18). Since the fumigator is not restricted to a single activity during the fumigation, the total exposure from doing all fumigator activities as well as the fumigator doing tent crew activities were also estimated. The combined short-term exposures were 0.0377 mg/kg/day (all fumigator activities) and 1.1699 mg/kg/day (fumigator and tent crew activities). The short-term exposures of the tent crew ranged from 0.0404 mg/kg/day (ground snake removal) to 1.1322 mg/kg/day (general detarping).

For repeated exposures at the submaximal application rate, the exposures were based on the mean air concentrations from the studies. The intermediate exposures ranged from 0.000002 mg/kg/day (closing structures) to 0.311 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.0131 mg/kg/day (ground snake removal) to 0.2912 mg/kg/day (general detarping) for the tent crew (Table 18). The annual exposures ranged from 0.0000008 mg/kg/day (closing structures) to 0.154 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.0065 mg/kg/day (ground snake removal) to 0.1433 mg/kg/day (general detarping) for the tent crew. The lifetime exposures ranged from 0.0000004 mg/kg/day (closing structures) to 0.0821 mg/kg/day (fumigator and tent crew activities) for fumigators, and from 0.0034

[7] U.S. EPA definitions for worker/residential exposure duration are: short-term (1 day to 1 month), intermediate (1 to 6 months), and long-term (several months to lifetime) (U.S. EPA, 2001b).

mg/kg/day (ground snake removal) to 0.0765 mg/kg/day (general detarping) for the tent crew. At the maximal application rate, the exposures were 14.5 times that of the submaximal rate for all exposure groups. The assumption was that exposure was directly proportional to the application rate (**Appendix A**).

IV.B.1.b. Non-food Commodity Fumigation - Handler

For non-food commodity fumigation, the handler exposures applied to all commodity workers (i.e. fumigators and commodity post-fumigation handlers) and were assumed at 5 ppm, since there were no monitoring studies at DPR. Furthermore, the worker exposure duration was assumed at 8 hours per day but only one application per year since this use is relatively rare as discussed in **Appendix A**. The acute, annual, and lifetime exposures for these workers were 0.429 mg/kg/day, 0.001 mg/kg/day, and 0.001 mg/kg/day, respectively (Table 18).

IV.B.2. Residential and Bystander Exposures

The exposures of residents reentering fumigated homes were based on air monitoring studies for 7 homes. For bystander exposures during the application of sulfuryl fluoride, they were estimated from ambient air monitoring from actual fumigations. During aeration with TRAP methods, the bystander exposures were estimated from monitoring data of workers doing general detarping activities. The bystander exposures for the Stack aeration, on the other hand, were based on monitoring data for the method. The bystander exposure at a non-food use commodity fumigation was based on the 5 ppm exposure limit. Under each scenario, exposures were determined for different age groups using age-dependent inhalation rates, hours of exposure, and body weight. For all scenarios, children who are 1-2 years old had the highest exposure because of their higher inhalation rate (m^3/hr/kg, Table 8 in **Appendix A**).

IV.B.2.a. Structural Fumigation – Residents

Exposures were estimated for residents returning to homes after clearance for occupation using monitoring data collected following minimum clearance requirement (Table 19). The data showed continuous dissipation of sulfuryl fluoride over a 7-day period (Figure 5 in **Appendix A**). The acute, short-term, and annual absorbed doses were estimated as an upper bound during sulfuryl fluoride dissipation following clearance. The lifetime absorbed dose was the mean air concentration of the interval of 0-7 days following clearance. For acute exposure, the range of exposures was 0.20 mg/kg/day (15-18 years old) to 0.52 mg/kg/day (1-2 years old). The range of short-term exposures was 0.05 mg/kg/day (12-18 years) to 0.12 mg/kg/day (1-2 years old). The range of annual exposures was 0.0009 mg/kg/day (15-18 years) to 0.0024 mg/kg/day (1-2 years old). The lifetime exposure for adults was 0.0002 mg/kg/day.

IV.B.2.b. Structural Fumigation - Bystanders

Bystander exposures during fumigant application and aeration phases were estimated based on air monitoring studies (Tables 20-22). During the application phase, peak sulfuryl fluoride was detected in the ambient air after application and dissipated over a 24-hour period

(Figure 6 in **Appendix A**). The bystander exposures were estimated for the first 12-hour, and overall 24-hour period (Table 20). For all age groups and at submaximal application rate, the acute-12 hour exposures ranged from 0.14 mg/kg/day (15-18 years old) to 0.34 mg/kg/day (1-2 years old). The 24-hour overall exposures were 0.2 mg/kg/day (15-18 years old) to 0.48 mg/kg/day (1-2 years old). The annual exposures (1 day per year) ranged from 0.0006 mg/kg/day (12-18 years old, adult) to 0.0013 mg/kg/day (1-2 years old). The lifetime exposure of adults was 0.0002 mg/kg/day. The exposures for maximal application rate were 10 times that of the submaximal rate (**Appendix A**).

On the first day of aeration, the bystanders were exposed primarily during the first few hours. The exposures were estimated based on monitoring studies for two aeration methods[8] with the Stack plan resulting in lower exposures (see **Appendix A** for description of these methods). Using the TRAP method for aeration, the acute 2-hour exposures ranged from 0.36 mg/kg/day (15-18 years old) to 0.85 mg/kg/day (1-2 years old) (Table 21). The annual exposures ranged from 0.001 mg/kg/day (12 years old to adult) to 0.002 mg/kg/day (all less than 12 years old). The lifetime exposure of adults was 0.0002 mg/kg/day. The exposures for maximal application rate were 14.5 times that of the submaximal rate.

Using the Stack plan, the peak exposure was after 1 hour in a 4-hour period (Table 22). The overall exposures were lower than those for the TRAP (Tables 21 and 22). It should be noted that the Stack plan is not current practice in California. The acute 1-hour exposures ranged from 0.05 mg/kg/day (15-18 years old) to 0.13 mg/kg/day (1-2 years old). For the 4-hour exposure period, the acute exposures ranged from 0.06 mg/kg/day (15-18 years old) to 0.14 mg/kg/day (1-2 years old). The annual exposures ranged from 0.00016 mg/kg/day (15-18 years) to 0.00038 mg/kg/day (1-2 years old). The lifetime exposure of adults was 0.00005 mg/kg/day. The exposures for maximal application rate were 10 times that of the submaximal rate.

IV.B.2.c. Non-food Commodity Fumigation – Bystanders

For non-food commodity fumigation, the bystander exposures were assumed to occur for only one day and at 5 ppm as assumed for the handlers. The acute 24-hour exposures ranged from 0.89 mg/kg/day (15-18 years old) to 2.10 mg/kg/day (1-2 years old) (Table 23). The annual exposures ranged from 0.0024 mg/kg/day (15-18 years old) to 0.0058 mg/kg/day (1-2 years old). The lifetime exposure of adults was 0.002 mg/kg/day.

[8] TRAP=Tarpaulin Removal and Aeration Plan, a standard aeration practice in California. The Stack plan is an alternative aeration procedure. The main difference is the longer aeration time with the Stack plan. Details of these methods are in Appendix A.

Table 18. Sulfuryl fluoride exposure estimates of structural and non-food commodity fumigation workers.[a]

Exposure Groups	Short-term	Intermediate	Annual	Lifetime
A. Structural Fumigation				
Exposure duration	0.17 to 3.73 hrs/day 1 to 7 days	7 days to < 1 year	49 weeks/year	40 years/ 75 years
1. Fumigators at Submaximal Rate	**Absorbed Dose (mg/kg/day)**			
Introducing fumigant	0.029	0.0112	0.006	0.0032
Opening structure	0.0001	0.000035	0.000017	0.000009
Closing	0.000006	0.000002	0.0000008	0.0000004
Testing for clearance[b]	0.0086	0.0086	0.0046	0.0025
Total activities	0.0377	0.0199	0.0107	0.0057
Fumigator +tent crew	1.1699	0.311	0.154	0.0821
2. Tent Crew at Submaximal Rate				
Ground seam opening	0.3047	0.0503	0.0247	0.0132
Roof seam opening	0.307	0.0716	0.0353	0.0188
Ground snake removal	0.0404	0.0131	0.0065	0.0034
Tarpaulin folding	0.0554	0.0157	0.0077	0.0041
General detarping	1.1322	0.2912	0.1433	0.0765
3. Fumigators at Maximal Rate				
Introducing fumigant	0.4203	0.163	0.0875	0.0467
Opening structure	0.0015	0.0005	0.0002	0.0001
Closing	0.000089	0.000023	0.000011	0.000006
Testing for clearance[b]	0.0086	0.0086	0.0046	0.0025
Total activities	0.43	0.172	0.092	0.049
Fumigator +tent crew	16.85	4.39	2.17	1.16
4. Tent Crew Maximal Rate				
Ground seam opening	4.418	0.729	0.359	0.191
Roof seam opening	4.451	1.039	0.511	0.273
Ground snake removal	0.586	0.190	0.094	0.050
Tarpaulin folding	0.803	0.227	0.112	0.060
General detarping	16.417	4.222	2.078	1.109
B. Non-food Commodity Fumigation				
Exposure duration	**Acute** 8 hours/day		**Annual** 1 day/ year	**Lifetime** 1 day for 40 years in 75 years
Handler[b,c]	0.429	NA	0.001	0.001

a/ Based on Table 7a and 7b from **Appendix A**. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, respiratory protection factor (when applicable), and an absorption factor of 18%. Exposures at maximal application rate were assumed to be 14.5 times those from the submaximal rate.

b/ Based on the maximal air concentration of 5 ppm.

c/ Non-food Commodity Handler values would apply to all commodity workers (i.e. fumigators and commodity post-fumigation handlers) assuming on-site air levels do not exceed 5 ppm.

Table 19. Sulfuryl fluoride exposure estimates for residents following clearance of fumigated homes.[a]

Resident	Acute absorbed dose (mg/kg/day)	Short-term absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	14-17 hours during the first 24 hours of reoccupation	1 to 7 days during reoccupation	≤ 7 days/year	≤ 7 days/year for 57 of 75 years
Age (years)				
<1	0.47	0.11	0.0021	NA
1-2	0.52	0.12	0.0024	NA
3-5	0.44	0.10	0.0020	NA
6-8	0.34	0.08	0.0015	NA
9-11	0.30	0.07	0.0014	NA
12-14	0.23	0.05	0.0010	NA
15-18	0.20	0.05	0.0009	NA
Adult	0.24	0.06	0.0011	0.0002

a/ Based on Table 13 from **Appendix A**. NA=not applicable. Exposure was based on air monitoring data collected during the first 48 hours following minimum clearance requirements. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18%.

Table 20. Sulfuryl fluoride exposure estimates for bystanders at a structural fumigation site during the application phase.[a]

Bystander (Age)	Acute-12 hours absorbed dose (mg/kg/day)	Acute-24 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	12 hours/day	24 hours/day	1 day/year	1 day/year for 57 of 75 years
Structural Fumigation at Submaximal Rate				
<1	0.30	0.42	0.0012	NA
1-2	0.34	0.48	0.0013	NA
3-5	0.29	0.41	0.0011	NA
6-8	0.24	0.34	0.0009	NA
9-11	0.23	0.33	0.0009	NA
12-14	0.17	0.23	0.0006	NA
15-18	0.14	0.20	0.0006	NA
Adult	0.17	0.24	0.0007	0.0002
Structural Fumigation at Maximal Rate				
<1	3.00	4.22	0.012	NA
1-2	3.40	4.78	0.013	NA
3-5	2.93	4.12	0.011	NA
6-8	2.40	3.37	0.009	NA
9-11	2.31	3.25	0.009	NA
12-14	1.65	2.32	0.006	NA
15-18	1.42	2.00	0.005	NA
Adult	1.71	2.41	0.007	0.002

a/ Based on Table 14a and 14b from **Appendix A**. NA=not applicable. Exposure was based on air monitoring data from structural fumigation. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18%. Exposures at maximal application rate were assumed to be 10 times those for the submaximal rate.

Table 21. Sulfuryl fluoride exposure estimates for bystanders at a structural fumigation site during the aeration phase using TRAP method.[a]

Bystander (Age)	Acute- 2 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	2 hours/day for 1 day	1 day per year	1 day/year for 75 years
Structural Fumigation at Submaximal Rate			
<1	0.77	0.002	NA
1-2	0.85	0.002	NA
3-5	0.75	0.002	NA
6-8	0.61	0.002	NA
9-11	0.58	0.002	NA
12-14	0.41	0.001	NA
15-18	0.36	0.001	NA
Adult	0.43	0.001	0.0002
Structural Fumigation at Maximal Rate			
<1	11.11	0.03	NA
1-2	12.28	0.03	NA
3-5	10.83	0.03	NA
6-8	8.84	0.02	NA
9-11	8.42	0.02	NA
12-14	6.01	0.02	NA
15-18	5.17	0.01	NA
Adult	6.24	0.02	0.003

a/ Based on Table 15a and 15b from **Appendix A**. NA=not applicable. Exposure was based on air monitoring data from structural fumigation. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18%. Exposures at maximal application rate were assumed to be 14.5-fold of those for the submaximal rate. TRAP=Tarpaulin Removal and Aeration Plan.

Table 22. Sulfuryl fluoride exposure estimates for bystanders at a structural fumigation site during the aeration phase using Stack plan.[a]

Bystander (Age)	Acute-1 hour absorbed dose (mg/kg/day)	Acute-4 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	1 hour/day	4 hours/day	1 day in 1 year	1 day/year for 57 of 75 years
Structural Fumigation at Submaximal Rate				
<1	0.11	0.12	0.00033	NA
1-2	0.13	0.14	0.00038	NA
3-5	0.11	0.12	0.00033	NA
6-8	0.09	0.10	0.00028	NA
9-11	0.09	0.10	0.00026	NA
12-14	0.06	0.07	0.00019	NA
15-18	0.05	0.06	0.00016	NA
Adult	0.07	0.07	0.00019	0.00005
Structural Fumigation at Maximal Rate				
<1	1.12	1.21	0.0033	NA
1-2	1.28	1.37	0.0038	NA
3-5	1.11	1.19	0.0033	NA
6-8	0.94	1.01	0.0028	NA
9-11	0.90	0.97	0.0027	NA
12-14	0.63	0.68	0.0019	NA
15-18	0.55	0.59	0.0016	NA
Adult	0.66	0.71	0.0019	0.0005

a/ Based on Table 16a and 16b from **Appendix A**. NA=not applicable. Exposure was based on air monitoring data from structural fumigation. The absorbed dose took into account of the exposure duration, body weight, inhalation rate, and an absorption factor of 18%. Exposures at the maximal application rate were assumed to be 10 times those for the submaximal rate.

Table 23. Sulfuryl fluoride exposure estimates for bystanders at or near a non-food commodity fumigation site.[a]

Bystander (Age)	Acute-24 hours absorbed dose (mg/kg/day)	Annual absorbed dose (mg/kg/day)	Lifetime absorbed dose (mg/kg/day)
Exposure duration	24 hours/day for 1 day	1 day/year	1 day/year for 57 of 75 years
<1	1.90	0.0052	NA
1-2	2.10	0.0058	NA
3-5	1.85	0.0051	NA
6-8	1.51	0.0041	NA
9-11	1.44	0.0039	NA
12-14	1.03	0.0028	NA
15-18	0.89	0.0024	NA
Adult	1.07	0.0029	0.002

a/ Based on Table 17 from **Appendix A**. NA=not applicable. Exposures were based on 5 ppm as the maximum level allowed on the label. The absorbed dose took into account the exposure duration, body weight, inhalation rate, and an absorption factor of 18%.

IV.C. RISK CHARACTERIZATION

The potential health risk associated with the use of sulfuryl fluoride was considered for occupational, bystander, and residential inhalation exposures. Non-oncogenic effects were characterized in terms of a margin of exposure (MOE), defined as the ratio of the NOEL from animal or human studies to the estimated human exposure levels. The NOELs in absorbed doses are listed in Table 17, and the exposure levels for the various exposure scenarios are presented in Tables 18 to 23. Since the exposure durations in the toxicology studies are defined differently than some of the scenarios in the Exposure Assessment (**Appendix A**), the applicable NOELs for the exposure durations are presented in Table 24.

In the selection of the NOELs, the important considerations were frequency of exposure (number of days per year) and dissipation characteristics. The acute NOEL was used to address the daily exposures (expressed as short-term exposures) of the fumigators and tent crews and peak exposures (expressed as acute exposures) of residents and bystanders of the structural fumigation as well as handlers and bystanders to commodity fumigation. The overall exposure of residents during the 7 days of reoccupation (short-term exposure) of treated home was not assessed since there was no toxicology study available with continuous dissipation of sulfuryl fluoride over this period. Repeated daily exposures occurred primarily with workers doing structural fumigation. The short-term exposures of fumigators and tent crews were also assessed using a 1-2 week NOEL since these workers could be exposed to sulfuryl fluoride on a weekly basis. Intermediate and annual exposures associated with this use were assessed using subchronic and chronic NOELs, respectively. Annual exposures based on 1 or 7 days of exposure (all residential and bystander exposures) were not assessed because they were considered acute exposures. The lifetime risk of sulfuryl fluoride exposure for all groups was not evaluated since sulfuryl fluoride has not been shown to be oncogenic in either humans or experimental animals.

The potential risk from exposure to sulfuryl fluoride was assessed with a comparison of margins of exposure to benchmarks or of air concentrations with the reference concentrations. For risk assessment under SB 950, DPR evaluates the exposure using a benchmark margin of exposure of 100 when the NOEL for non-oncogenic effects was based on animal data. This benchmark of 100 included an uncertainty factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variability. These uncertainty factors assume that the average human is 10 times more sensitive to the effects of a chemical than the most sensitive laboratory animal, and that a sensitive individual is 10 times more susceptible than an average individual (Davidson *et al.*, 1986; Dourson and Stara, 1983).

A higher benchmark of 1000, with an additional database uncertainty factor of 10-fold was considered for sulfuryl fluoride residential and bystander exposures in this document because of a data gap due to the requirement of a developmental neurotoxicity study by the U.S. EPA (U.S. EPA, 2004a). This factor would be applicable for all age groups as a general approach. Potential developmental neurotoxicity would likely to have greater impact on the fetus, infants, and young children with developing central nervous systems. In the dietary risk assessment for Profume®, the U.S. EPA applied the dietary reference concentration with this

additional 10-fold factor to the exposures of all age groups.

For potential listing under AB 1807 as a toxic air contaminant, ambient air exposures as represented by bystander exposures are compared to the reference concentrations. The listing criteria (California Code of Regulations, Title 3, Division 6, Section 6890) specifies that a pesticide shall be listed if the ambient air concentrations are greater than the following: (1) 10-fold below the reference concentration for pesticides with threshold effects, or (2) 10-fold below the negligible risk concentration. Based on criteria (1), exposures of concern are those higher than 1/10 of the reference concentration. Since the equation for reference concentration and MOEs are related, these were also scenarios where the MOEs for bystander exposures were less than 10,000.

IV.C.1. Occupational Exposure

IV.C.1.a. Structural Fumigation - Fumigators and Tent Crew

For structural fumigation using the submaximal rate of application, the MOEs for individual fumigator activities for all durations were greater than 100 (ranged from 120 to >10,000) (Table 25). For total fumigator activities, the acute, 1-2 week, and subchronic MOEs were greater than 100, but was 67 for chronic exposure. All MOEs for workers doing both fumigation and tent crew activities were less than 100 (range from 5 to 46). For the tent crew, the acute and 1-2 week MOEs were higher than 100 (range from 130 to 1337) for most activities, except for general detarping, ground seam opening, and roof seam opening where the MOEs were 6 to 48. For subchronic exposure, the MOEs ranged from 8 (general detarping) to 168 (ground snake removal). For chronic exposure, the MOEs ranged from 5 (general detarping) to 111 (ground snake removal).

At the maximal application rate, the MOEs for fumigators and tent crew were 14.5 times lower than those for submaximal rate, and were generally less than 100 except for scenarios with minimal exposures such as opening, closing, and testing activities for fumigators (Table 25). The MOEs for the tent crew were all less than 100.

IV.C.1.b. Non-food Commodity Fumigation - Handler

For handlers of non-food commodity fumigation, the MOE was 126 for acute exposure (Table 25).

IV.C.2. Resident and Bystander Exposures

IV.C.2.a. Structural Fumigation – Residents

For residents reoccupying fumigated homes after clearance, the acute MOEs ranged from 104 (1-2 years old) to 180 (9-11 years old) for younger children (Table 26). For the older children and adults, the acute MOEs ranged from 225 (adults) to 270 (15-18 years old).

IV.C.2.b. Structural Fumigation - Bystanders

For bystander exposures during submaximal rate application, the acute (first 12-hours) MOEs for bystanders ranged from 159 (1-2 years old) to 386 (15-18 years old) (Table 27). The MOEs for 24-hour exposure during the application phase ranged from 113 (1-2 years old) to 270 (15-18 years old). At the maximal application rate, the acute and short-term MOEs for all age groups were 10-fold lower than those for the submaximal rate, and were at or less than 38.

During aeration using the TRAP method after application at the submaximal application rate, the short-term MOEs for the bystanders ranged from 64 (1-2 years old) to 150 (15-18 years old) (Table 28). For aeration using the Stack method, the acute MOEs for the first hours ranged from 415 (1-2 years old) to 1080 (15-18 years old) (Table 28). Over the 2-hour period, the MOEs ranged from 386 (1-2 years old) to 900 (15-18 years old). At the maximal application for either aeration methods, the acute MOEs were at or less than 10 for the TRAP method, and at or less than 39 for the Stack method.

For both application and aeration phases, the estimated exposures as 24-hour time-weighted averages were much higher than the reference concentrations. Table 30 showed a comparison for infants, the highest exposed group, with the estimated exposure as much as 1418% (aeration using TRAP method) of the reference concentration for this group.

IV.C.2.c. Non-food Commodity Fumigation – Bystanders

The acute MOEs for bystanders near a commodity fumigation facility ranged from 26 (1-2 years old) to 61 (15-18 years old) (Table 29). At the assumed air level of 5 ppm and exposure for 24 hours, the estimated exposure was over 3000% of the reference concentration (Table 30).

Table 24. Exposure duration and applicable no-observed-effect levels (NOELs) for margin of exposure calculations.

Groups/tasks	Worker and Resident Exposure Durations		NOELs[a]
Structural fumigation			
Fumigator and tent crew	Short-term	Upper bound exposure values for ≤ 7 days	Acute 1-2 weeks
	Intermediate	Mean exposure values for ≥ 7 days to < 1 year	Subchronic
	Annual	Mean exposure values 49 weeks/year	Chronic
	Lifetime	40 years/75 years	NA
Resident after clearance for reentry	Acute-24 hours	14 to 17 hours on first day of reoccupation	Acute
	Short-term	7 days during reoccupation with continuous decay	NA
	Annual	7 days/year	NA
	Lifetime	7 days/year for 57 of 75 years	NA
Bystander during application	Acute- 12 hours	First 12 hours of application phase	Acute
	Acute- 24 hours	24 hours for 1 day	Acute
	Annual	1 day/year	NA
	Lifetime	1 day/year for 57 of 75 years	NA
Bystander during aeration using TRAP or Stack method	Acute-1 hour	1 hour/day (for Stack method only)	Acute
	Acute-2 and 4 hours	TRAP: 2 hours/day Stack: 4 hour/day	Acute
	Annual	1 day/year	NA
	Lifetime	1 day/year for 57 of 75 years	NA
Non-food Commodity Fumigation (Assume 5 ppm)			
Handler[b]	Acute- 8 hours	8 hours/day	Acute
	Annual	1 day/year	NA
	Lifetime	1 day for 40 years of 75 years	NA
Bystander	Acute-24 hours	24 hours for 1 day	Acute
	Annual	14-17 hours for 1 day in a year	NA
	Lifetime	1 day/year for 57 of 75 years	NA

a/ The NOELs and endpoints are listed in Table 17. The acute NOEL was 300 mg/kg/day (absorbed dose of 54 mg/kg/day) for no FOB effects in rats after two days of exposure (Albee *et al*., 1993a). The 1-2 weeks NOEL was 40 mg/kg/day (absorbed dose of 7.2 mg/kg/day) for brain lesions in rabbits after 2 weeks of exposure (Eisenbrandt *et al*., 1985). The subchronic NOEL was 12 mg/kg/day (absorbed dose of 2.2 mg/kg/day) for brain lesions in rabbits after 13 weeks of exposure (Nitschke et al., 1987b). The chronic NOEL was 4 mg/kg/day (absorbed dose of 0.72 mg/kg/day) for lung pathology in rats in a 2-generation reproductive toxicity study (Breslin *et al*., 1992). NA=there is no applicable NOEL for the exposure duration.

b/ Commodity Handler values would apply to all commodity workers (i.e. fumigators and commodity post-fumigation handlers) assuming on-site air levels do not exceed 5 ppm.

Table 25. Margins of exposure (MOE) for sulfuryl fluoride exposure estimates of structural and non-food commodity fumigation workers.[a]

Work Task	Acute MOE	1-2 weeks MOE	Subchronic MOE	Chronic MOE
Structural Fumigation at Submaximal Rate				
Fumigators				
Introducing fumigant	1862	248	196	120
Opening structure	>10,000	>10,000	>10,000	>10,000
Closing	>10,000	>10,000	>10,000	>10,000
Testing for clearance	6279	837	256	157
Total activities	1432	191	111	67
Fumigator +tent crew	46	6	7	5
Tent Crew				
Ground seam opening	177	24	44	29
Roof seam opening	176	23	31	20
Ground snake removal	1337	178	168	111
Tarpaulin folding	975	130	140	94
General detarping	48	6	8	5
Structural Fumigation at Maximal Rate				
Fumigators				
Introducing fumigant	128	17	13	8
Opening structure	>10,000	4800	4400	3600
Closing structure	>10,000	>10,000	>10,000	>10,000
Testing for clearance	6279	837	256	157
Total activities	126	17	13	8
Fumigator +tent crew	3	0.4	1	0.8
Tent Crew				
Ground seam opening	12	2	3	2
Roof seam opening	12	2	2	1
Ground snake removal	92	12	12	8
Tarpaulin folding	67	9	10	6
General detarping	3	0.4	1	0.3
Non-food Commodity Fumigation				
Handlers	126	NA	NA	NA

a/ Based on exposure values in Table 18 and applicable NOELs in Table 24.

Table 26. Margins of exposure (MOEs) for residents following clearance of fumigated homes.[a]

Resident (Age)	Acute 24-hour MOE
<1 years	115
1-2 years	104
3-5 years	123
6-8 years	159
9-11 years	180
12-14 years	235
15-18 years	270
Adult	225

a/ Based on exposure values in Table 19 and applicable NOEL in Table 24.

Table 27. Margins of exposure (MOEs) for bystanders at a structural fumigation site during the application phase.[a]

Bystander (Age)	Acute 12-hour MOE	Acute 24-hour MOE
Structural Fumigation at Submaximal Rate		
<1 year	180	129
1-2 years	159	113
3-5 years	186	132
6-8 years	225	159
9-11 years	235	164
12-14 years	318	235
15-18 years	386	270
Adult	318	225
Structural Fumigation at Maximal Rate		
<1 year	18	13
1-2 years	16	11
3-5 years	18	13
6-8 years	23	16
9-11 years	23	17
12-14 years	33	23
15-18 years	38	27
Adult	32	22

a/ Based on exposure values in Table 20 and applicable NOEL in Table 24.

Table 28. Margins of exposure (MOEs) for bystanders at a structural fumigation site during the aeration phase using TRAP and Stack aeration methods.[a]

Bystander (Age)	TRAP aeration	Stack aeration	
	Acute 2-hour MOE	Acute 1-hour MOE	Acute 4-hour MOE
Structural Fumigation at Submaximal Rate			
<1 year	70	491	450
1-2 years	64	415	386
3-5 years	72	491	450
6-8 years	89	600	540
9-11 years	93	600	540
12-14 years	132	900	771
15-18 years	150	1080	900
Adult	126	771	771
Structural Fumigation at Maximal Rate			
<1 year	5	48	45
1-2 years	4	42	39
3-5 years	5	49	45
6-8 years	6	57	53
9-11 years	6	60	56
12-14 years	9	86	79
15-18 years	10	98	92
Adult	9	82	76

a/ Based on exposure values in Tables 21 and 22 and applicable NOEL in Table 24.

Table 29. Margins of exposure (MOEs) for bystanders at or near a non-food commodity fumigation site.[a]

Bystander (age)	Acute 24-hour MOE
<1 year	28
1-2 years	26
3-5 years	29
6-8 years	36
9-11 years	38
12-14 years	52
15-18 years	61
Adult	50

a/ Based on exposure values in Table 23 and applicable NOEL in Table 24.

Table 30. Comparison of infant bystander exposures with reference concentration.

Scenario	Air level[a]	Hours exposed[a]	Air level as 24-hour time-weighed average	% RfC[b]	MOE[c]
Structural Fumigation at Submaximal Rate					
Application phase					
First 12-hours	1.6 ppm	12	0.8 ppm	567%	180
24 hours	1.12 ppm	24	1.12 ppm	794%	129
Aeration phase TRAP method					
2 hours	24 ppm	2	24 ppm	1418%	70
Aeration phase Stack method					
1 hour	7.33 ppm	1	0.31 ppm	217%	491
2 hour	1.97 ppm	4	0.33 ppm	233%	450
Non-food Commodity Fumigation					
24 hours	5 ppm	24	5 ppm	3546%	28

a/ Based on information in Tables 14a, 15a, 16a, and 17 in Appendix A. The reference concentration for infants was 0.14 ppm (Table 17). The MOEs were those shown in Tables 27-29.

IV.D. COMPARISON WITH U.S. ENVIRONMENTAL PROTECTION AGENCY RISK ASSESSMENT

The risk assessment conducted in this document was compared with the U.S. EPA risk assessment for ProFume® (U.S. EPA, 2004 b and c) and Reregistration Eligibility Document for Vikane® (U.S. EPA, 1993b).

IV.D.1. Hazard Identification and Reference Concentrations

The endpoints and NOELs selected by DPR were compared with those used by U.S. EPA in the establishment of food tolerances which represented the U.S. EPA most current values (U.S. EPA 2004 a, b, and c) as shown on Table 31. There were several differences:

1. DPR determined an acute inhalation NOEL from a 2-day study. While the NOEL was based on more than one day of exposure, DPR considered it appropriate to use since there are exposure scenarios where humans are exposed to sulfuryl fluoride on consecutive days at similar air concentrations, and the NOEL was comparable to those from single day exposures of a few hours. On the other hand, the U.S. EPA determined that there was no need to address inhalation risk from a single exposure because there was no toxicity endpoint from a single exposure.

2. While both U.S. EPA and DPR selected the same studies and same NOELs (in terms of ppm) to address repeated exposures of less than 1 year, the NOELs as mg/kg/day were different due to different default inhalation rates used for rabbits. The DPR and U.S. EPA inhalation rates for rabbits were 0.54 m^3/kg/day and 0.38 m^3/kg/day[9], respectively.

3. For chronic inhalation exposure, DPR selected the NOEL of 4 mg/kg/day from a 2-generation toxicity study with lung pathology as the endpoint. DPR considered this endpoint appropriate since similar effects were observed in other inhalation toxicity studies. In comparison, the U.S. EPA used a NOAEL (8.5 mg/kg/day) for brain lesions from a subchronic toxicity study and applied a 3-fold uncertainty factor (estimated chronic NOEL of 2.8 mg/kg/day) to derive the chronic reference dose and chronic reference concentration for dietary and inhalation exposures, respectively. The rationale was that the effect on the lung (U.S. EPA calculated NOAEL of 3.6 mg/kg/day) from the inhalation exposure was not appropriate to address dietary exposure. While DPR agreed with this rationale for dietary exposure, DPR considered the lung effect an appropriate

[9] This value was back-extrapolated from the U.S. EPA calculation assuming the following equation was used to convert the NOAEL of 30 ppm to 8.5 mg/kg/day. The rabbit inhalation rate (BR) was 0.38 m^3/kg/day and is consistent with the allometric equation for rabbits inhalation rate (I) in m^3/day=0.46 Body weight$^{0.8307}$ and body weight of 3 kg (U.S. EPA, 1988).

$$30 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 / \text{ppm} \times \text{BR}_{\text{rabbit}}\ \text{m}^3 / \text{kg} / \text{day} \times \frac{5 \text{ days}}{7 \text{ days}} \times \frac{6 \text{ hours}}{24 \text{ hours}} = 8.5 \text{ mg} / \text{kg} / \text{day}$$

It should be noted that the U.S. EPA no longer uses the above equation and the current rabbit mean inhalation rates are 0.55 m^3/kg/day and 0.52 m^3/kg/day for males and females, respectively, based on values provided in the 1994 document for reference concentration (U.S. EPA, 1994).

endpoint to address chronic inhalation exposure.

IV.D.2. Exposure Assessment

The exposure assessments conducted by U.S. EPA (U.S. EPA, 1993b and 2004c) and DPR showed differences in exposure estimates mainly due to different approaches/assumptions used in the absence of adequate exposure data. Also, DPR based its estimates on use scenarios in California while the U.S. EPA considered exposures at a national level. The following are some of the differences:

1. For structural fumigation, the U.S. EPA estimated worker exposures to Vikane® were stated as 0.08 ppm for fumigator and 0.17 ppm for tent workers. In comparison, DPR calculated exposures for individual and combined activities for fumigators and tent workers with a wide range of exposure levels (**Appendix A**).

2. For structural fumigation, the U.S. EPA stated that risks to residents returning to fumigated homes were negligible (U.S. EPA, 2004c). In comparison, DPR calculated exposures for residents upon reentry as well as bystander exposures during application and aeration phases. Some of these exposures were significant and lead to MOEs of less than 100 (Tables 26 to 28).

3. For non-food commodity fumigation with Vikane®, the U.S. EPA did not estimate exposures for handlers or bystanders. DPR used the limit of 5 ppm to estimate the exposures for these groups.

IV.D.3 Risk Characterization

A comparison of margins of exposures showed significant differences between DPR and the U.S. EPA (Table 32). These differences were primarily the result of differences in the exposure estimates. It should be noted that U.S. EPA applied the dietary reference concentration in the dietary risk assessment for the food-use label (Profume®) for all age groups. The residential reference concentrations were, however, not used in the U.S. EPA risk assessments since residential and bystander inhalation exposures for the use of Vikane® were not estimated.

Table 31. Comparison of critical no-observed-effect levels (NOELs) and endpoints for risk characterization between the Department of Pesticide Regulation and U.S. Environmental Protection Agency.[a]

DPR		USEPA	
Duration	**NOEL and endpoint**	**Duration**	**NOEL and endpoint**
Acute	2-day rat: no FOB effect (Albee *et al*., 1993a) NOEL= 300 ppm (300 mg/kg/day) Occupational RfC=3 mg/kg/day (UF=100) Residential/Bystander RfC=0.3 mg/kg/day (UF=1000)	No toxicity endpoint for single exposure	
1-2 weeks	2-week rabbit: brain lesions (Eisenbrandt *et al*., 1985) NOEL= 100 ppm (40 mg/kg/day) Occupational RfC=0.4 mg/kg/day (UF=100) Residential/Bystander RfC=0.04 mg/kg/day (UF=1000)	Short-term 1-30 days	2-week rabbit: brain lesions (Eisenbrandt *et al*., 1985) NOAEL = 100 ppm (30 mg/kg/day) Occupational RfC=0.30 mg/kg/day (UF=100) Residential RfC= 0.03 mg/kg/day (UF=1000)
Sub-chronic	90-day rabbit: brain vacuoles (Nitschke *et al*., 1987b) NOEL=30 ppm (12 mg/kg/day) Occupational RfC=0.12 mg/kg/day (UF=100) Residential/Bystander RfC=0.012 mg/kg/day (UF=1000)	Inter-mediate term (1-6 months)	90-day rabbit: brain vacuoles (Nitschke *et al*., 1987b) NOAEL=30 ppm (8.5 mg/kg/day) Occupational RfC=0.085 mg/kg/day (UF=100) Residential RfC=0.0085 mg/kg/day (UF=1000)
Chronic	2-generation rat: lung pathology (Breslin *et al*., 1992) NOEL=5 ppm (4 mg/kg/day) Occupational RfC=0.04 mg/kg/day (UF=100) Residential/Bystander RfC=0.004 mg/kg/day (UF=1000)	Long-term (>6 months)	90-day rabbit: brain vacuoles (Nitschke *et al*., 1987b) NOAEL=30 ppm (8.5 mg/kg/day) Occupational RfC=0.028 mg/kg/day (UF=300) Residential RfC=0.0028 mg/kg/day (UF=3000)

a/ When the NOEL in terms of ppm is the same for both DPR and U.S. EPA, differences in the dosages were due to differences in the default inhalation rates for the experimental animals used. The DPR default inhalation rates for rats and rabbits are 0.96 m^3/kg/day and 0.54 m^3/kg/day, respectively. The U.S. EPA default inhalation rate for rabbit was 0.38 m^3/kg/day (see footnote 9). For the reference concentrations (RfC), the uncertainty factors (UF) were 100 (10x each for intraspecies and interspecies extrapolation), 300 (10x each for intraspecies and interspecies extrapolation, 3x for subchronic to chronic NOAEL extrapolation), 1000 (10X each for intraspecies and interspecies extrapolation, and 10x for developmental neurotoxicity study data gap), and 3000 (10X each for intraspecies and interspecies extrapolation, 3x for subchronic to chronic NOAEL extrapolation, and 10x for developmental neurotoxicity study data gap). These NOELs were not corrected for absorption.

Table 32. Comparison of margins of exposure (MOEs) from the Department of Pesticide Regulation and U.S. Environmental Protection Agency.

Uses	DPR MOEs[a]		U.S. EPA MOEs[b]
Structural fumigation			
Fumigator	Submaximal rate: Acute: 46 to >10,000 1-2 week: 23 to >10,000 Subchronic: 6 to >10,000 Chronic: 5 to >10,000	Maximal rate: Acute: 3 to >10,000 1-2 week: 2 to >10,000 Subchronic: <1 to >10,000 Chronic: <1 to >10,000	Short-term: 440 Intermediate and long term: 130
Tent Crew	Submaximal rate: Acute: 48 to 1337 1-2 week: 25 to 550 Subchronic: 7 to 151 Chronic: 5 to 111	Maximal rate: Acute: 3 to 92 1-2 week: 2 to 38 Subchronic: <1 to 10 Chronic: <1 to 8	Short-term: 210 Intermediate and long term: 60
Resident-reentry	Acute: 104 to 270		Risk stated as negligible, MOE not given in risk assessment
Bystander-application	Submaximal rate: Acute 12 hours: 159 to 386	Maximal rate: Acute 12 hours: 16 to 38	Not assessed
Bystander-aeration	TRAP aeration Submaximal rate: Acute 1 hour: 64 to 150 Maximal rate: Acute 1 hour: 4 to 10	Stack aeration Submaximal rate: Acute 1 hour: 415 to 1080 Maximal rate: Acute: 42 to 98	Not assessed
Non-food Commodity fumigation			
Handlers	Acute: 126		Not assessed
Bystander	Acute: 26 to 61		Not assessed

a/ MOEs from Tables 25 to 29.
b/ U.S. EPA, 1993b and 2004c.

V. RISK APPRAISAL

V.A. INTRODUCTION

The human health risk assessment of sulfuryl fluoride was conducted for occupational, residential, and bystander exposures. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that adverse effects of a substance will occur under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. The degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment of sulfuryl fluoride are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION

The uncertainties associated with the selection of the endpoints and the NOELs have already been discussed under **IV.A. HAZARD IDENTIFICATION**. The critical and most sensitive endpoint for acute, 1-2 weeks of exposure, and subchronic exposures was neurotoxicity. This endpoint, in particular vacuolation in brain tissues, is also of concern by the U.S. EPA (U.S. EPA, 2004b and c). The critical endpoint for chronic exposure was lung effects (pathology, alveolar macrophage aggregates) in the rat (Breslin *et al*., 1992). DPR considered these effects relevant since they were the result of inhalation exposure, treatment related and observed in the dog (Table 14). The NOEL for this endpoint is lower than that for brain lesions in the chronic toxicity studies. In addition to the toxicological endpoints identified, the potential of sulfuryl fluoride to cause developmental neurotoxicity has not been studied. This potential stemmed from the observation of vacuolation in the adult brain tissue of several species after exposure to sulfuryl fluoride. Since the U.S. EPA waived the developmental neurotoxicity study requirement (Dellarco and Baetcke, 2004), it is not known if the NOEL for this endpoint would be higher or lower than those for neurotoxicity in the adult. In the absence of such a study, the concern will be addressed using an additional uncertainty factor (see discussion in **V.E.1. Pre- and Post-natal Sensitivity**). In addition, studies on the mechanism of action, effects of short exposure durations, toxicity of metabolites especially with regard to fluoride contribution to non-dental endpoints, and potential additional toxicity with chloropicrin are needed for further hazard identification of sulfuryl fluoride.

With regard to specific critical NOELs used to calculate the MOEs, there was some uncertainty on the magnitude of the acute NOEL. This NOEL was selected from a 2-day (6 hours/day) study (Albee *et al*., 1993 a and b) specifically designed to evaluate the neurotoxicity of sulfuryl fluoride after two-days of exposure. At the highest dose (300 ppm) tested, there were no treatment-related effects observed. There were two related issues in the use of this NOEL for acute exposure: derivation of a one-day NOEL, and application of this NOEL for the MOE

calculation. The Albee *et a*l study (1993) was the only study of sufficient quality to be considered for the derivation of a critical NOEL. DPR recognizes that this NOEL was for a two-day study but consideration of other studies supported this NOEL as a single day NOEL. The DPR calculates the NOEL as a daily dosage (300 mg/kg/day) as shown in the following equation:

$$300 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 / \text{ppm} \times 0.96 \text{ m}^3 / \text{kg} / \text{day} \times \frac{6 \text{ hours}}{24 \text{ hours}} = 300 \text{ mg} / \text{kg} / \text{day}$$

In comparison, the registrant used the same NOEL (300 ppm) and asserted that the daily dosage should be 567 mg/kg/day (Wright *et al*., 2003; Dow AgroSciences, 2004). This calculation assumed that the two 6-hour separate exposure periods was equivalent to a single 12-hour exposure in 30 hours based on a certain dose-time relationship between these two durations of exposure. This 30-hour duration was then used to calculate the equivalent NOEL for a 24-hour time-weighted-average NOEL as shown by the following equation.

$$300 \text{ ppm} \times 4.17 \text{ mg} / \text{m}^3 / \text{ppm} \times 1.13 \text{ m}^3 / \text{kg} / \text{day} \times \frac{0.5 \text{ days}}{1.25 \text{ days}} = 567 \text{ mg} / \text{kg} / \text{day}$$

This approach used by the registrant resulted in a 24-hour NOEL (567 mg/kg/day) that is 1.9-fold higher than that (300 mg/kg/day) calculated by DPR. When compared to single dose studies, the registrant calculated NOEL might be too high (Table 4). Acute toxicity study in rats reported lethargy after 4-hour exposure to 750 ppm (500 mg/kg/day) (Miller *et al*., 1980). Morbidity and death between 2nd and 6th dose were observed in rats exposed to 600 ppm (600 mg/kg/day) (Eisenbrandt *et al*., 1985). Therefore, DPR considers 300 mg/kg/day as a reasonable NOEL to address acute exposure scenarios, given the limitations in the toxicology database.

The application of this acute NOEL based on continuous 6-hours exposure to fewer hours or scenarios of declining air concentration resulted in uncertainty to the risk estimates (further discussion is in **V.D. RISK CHARACTERIZATION**). This uncertainty is minimized to a limited extent by addressing peak exposure periods as well as the entire measured dissipation period. Additional toxicology studies are needed to determine the toxicity of few hours to 1-day exposure scenarios.

For repeated exposures, the NOELs were amortized to account for more than 5 days per week exposure since the label did not specifically limit the exposure to 5 days per week or number of weeks. In addition, amortization was a means to reflect a lower potential NOEL due to repeated weekly exposures. In practice, workers are more likely to be exposed for several consecutive weeks during the year. While the use of the 2-week NOEL may overestimate the risk for 1-week only exposures, it actually underestimates the risk for repeated weekly exposures, up to 13 weeks. For 13 weeks of exposure, the MOE was calculated using a subchronic NOEL of 12 mg/kg/day (3.5-fold lower than the 2-week NOEL).

While the hazard identification discussed only the toxicity of sulfuryl fluoride, humans are exposed to chloropicrin at the same time. There were no toxicity studies conducted with

these compounds administered as mixtures. It is not known whether exposure to chloropicrin, an irritant, would result in enhanced sulfuryl fluoride toxicity, in particular pulmonary toxicity. DPR placed all products containing chloropicrin into reevaluation in 2001. Under the reevaluation, chloropicrin registrants are required to submit worker exposure studies and ambient air quality monitoring studies. DPR has also requested that the Air Resources Board conduct monitoring of an application site in 2004. A risk characterization document for chloropicrin is being prepared.

V.C. EXPOSURE ASSESSMENT

There were uncertainties associated with the estimated exposures since the database was limited and protective factors were use to compensate for the data uncertainties (more detailed discussion is in **Appendix A EXPOSURE APPRAISAL**). In order to refine the exposure estimates, additional studies should include: use of maximal application rate for structural fumigation, non-food commodity fumigation, longer (7 days) monitoring period and multiple sites in fumigated homes. For all these studies, sufficient number of replicates should be collected and all parts of the collected samples should be analyzed.

V.C.1. Occupational Expsoures

For workers of structural fumigation, there were sources of under- and over-estimation of exposures. The actual exposures could be higher if residues from the back section of charcoal tubes used to monitor exposure were included, or if there was improper use of Self-Contained Breathing Apparatus (SCBA). The worker exposures could be lower if the application rate was lower than those assumed for submaximal or maximal rates in this document.

For handlers in non-food commodity fumigation, the exposure was assumed at no higher than 5 ppm (an 8-hour time-weighted average, maximum allowed by the label) and only once per year. This exposure could be higher if food uses for sulfuryl fluoride are approved in California.

V.C.2. Residential and Bystander Exposures

For residents reentering the fumigated homes, the exposures could be underestimates due to lack of continuous monitoring of air concentration, slower dissipation of sulfuryl fluoride than assumed, longer indoor residence time than assumed, and more than one application per year to the home. At the same time, the latter three sources could result in the overestimation of risk under the conditions of more rapid gas dissipation, shorter indoor residence time, and less frequent than one application per year. Another source of overestimation was the assumption that reentry occurred according to label (6 or 8 hours) rather than typical practice of 1 day when the air concentration is lower. The bystander exposure during aeration of structural fumigation could be overestimated because it was based on the level for fumigation workers doing general detarping activities.

For bystanders near a non-food commodity fumigation facility, the exposure was

assumed to be no higher than 5 ppm in a 24-hour period and only 1 day per year. This exposure could be higher if the use was more frequent, especially when food uses are approved in California. On the other hand, the exposure could be lower with shorter time spent outdoors.

V.D. RISK CHARACTERIZATION

Uncertainties in the risk estimates are determined by limitations in the toxicology study designs to address specific exposure scenarios, and inadequate exposure data to derive the actual exposures for human exposure. To be health protective, conservative assumptions were made in the application of the NOELs and in the exposure estimates. The sources of over- and under-estimation of the risks already discussed are summarized in Table 33. Until additional data are available, the margins of exposure calculated and comparisons with reference concentrations in this document should be considered reasonable for use in risk management.

V.D.1. Margins of Exposure

For risk assessment under SB 950, the exposures were evaluated using the benchmark MOEs of 100 and 1000 for occupation, and bystander/residential exposures, respectively (**IV.C. RISK CHARACTERIZATION**). For sulfuryl fluoride, the 10-fold interspecies factor was considered appropriate, since the sensitivity of humans and laboratory animals to sulfuryl fluoride toxicity could not be compared due to the lack of adequate data on humans. For intraspecies variation in the response to the toxicity of sulfuryl fluoride, many factors can potentially contribute to the variation. Among these are age, gender, genetic disposition, health and nutritional statuses, and environmental factors. However, there were insufficient data to quantify these variations. Similarly, the concern for developmental neurotoxicity was addressed with a default uncertainty factor of 10-fold. These factors should be assumed adequate until additional data become available.

There was a large range of MOEs for workers depending on work activities (Table 25). The MOEs for opening and closing structures were greater than 10,000, while they were less than 100 for some fumigator and tent crew activities (Table 25). For these scenarios, it is unlikely that more comprehensive acute toxicity studies of less than 6 hours would significantly increase the MOE to meet the benchmark level. Current data from acute LC_{50}-type studies showed NOELs in the same range as the critical NOEL based on 6 hours of exposure (Table 4). On the other hand, the MOEs could be increased or decreased with additional exposure data.

Table 33. Sources of over- and under-estimation of risks for sulfuryl fluoride exposure.

Scenarios	Exposure	NOEL[a]	Risk is overestimated if:	Risk is underestimated if:
Fumigator workers and tent crew	**Acute** 0.17 to 3.73 hrs	6 hours	NOEL is higher for < 6 hrs exposure. Less than sub or maximal application rates were used.	Exposure is higher by including back sections of monitoring tubes and improper use of SCBA.
	Short-term 1 to 7 days	2 weeks	Exposure is less than sub or maximal rates, and is for shorter duration than the NOEL.	NOEL is lower for longer than NOEL duration. Exposure is higher due to back sections and SCBA concerns.
	Intermediate 7 day to < 1 m	13 weeks		
	Chronic 1 year	2 years		
Residential reentry	**Acute** SF level: declining over 2 days Duration: 24 hours	6 hours	NOEL is higher when there is continuous SF decline. Exposure is lower from more rapid dissipation, shorter indoor time, longer reentry time, and fewer fumigation.	Exposure is higher due to slower dissipation, longer residence time, and more than once a year fumigation.
Bystander during application	**Acute** SF level: Constant on 1st 12 hours, loss on 15th hour Duration: 24 hours/day	6 hours	NOEL is higher for the second 12-hours with continuous decline. Exposure is lower due to fewer hours outdoor.	NOEL is lower for 12-hours of exposure.
Bystander during TARP method aeration	**Acute** SF level: Peak in 2 hours Duration: 2 hours	6 hours	NOEL is higher for 2 hours of exposure. Exposure is lower than assumed in detarping activities	
Bystander during Stack method aeration	**Acute** SF level: Peak 1 hour, then decline, Duration: 4 hours	6 hours	NOEL is higher for 1 or 4 hours of exposure. Exposure is lower than assumed in general detarping activities	
Non-food commodity fumigation-Handlers	**Acute** SF level: 5 ppm Duration: 8 hours in 1day	6 hours	Exposure is lower if actual is lower than 5 ppm maximum allowed on the label	NOEL is lower for > 6 hours. Exposure is higher for or more than once a year use.
Non-food commodity fumigation-Bystander	**Acute** SF level: 5 ppm Duration: 24 hours	6 hours	NOEL is higher for the second 12-hours with continuous SF decline. Exposure is lower, and fewer hours outdoor per day.	NOEL is lower for the first 12-hours. Exposure is higher for more than once a year use.

a/ The duration of the toxicology studies. SF=sulfuryl fluoride.

For adult residential exposures to structural fumigation (reentry, application, and aeration) at submaximal application rate, the acute MOEs for peak sulfuryl fluoride concentrations were generally greater than 100 (Tables 26 to 28). However, the MOEs for young children were about 100, much lower than the benchmark of 1000. A higher MOE might be achieved if the NOEL was based on studies conducted with declining sulfuryl fluoride concentration, although it is unlikely to be 10-fold higher than the current acute NOEL. The exposure estimates for bystanders could be refined with monitoring data to address the assumptions used, such as 24 hours of indoor and outdoor exposure, and exposure at air levels experienced by workers doing detarping activities. In addition, the Stack aeration method with lower bystander exposures, instead of TRAP aeration, might be considered for California. As shown in Table 28, there was about a 7-fold difference in the MOEs between these two methods. For bystanders to non-food commodity fumigation, the MOEs were all less than 100 (Table 29). These were based on the assumption of 24 hours of continuous exposures at 5 ppm. These MOEs would likely to be changed with actual monitoring data for indoor and outdoor air levels of sulfuryl fluoride.

V.D.2. Reference Concentrations

Since the bystander exposures showed MOEs of less than 10,000 (Tables 27-29), they exceeded the limit of no more than 1/10 of the reference concentrations (Table 17). Sulfuryl fluoride would, therefore, meet the listing criteria under AB 1807 and will be reviewed by the Scientific Review Panel for AB 1807.

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

V.E.1. Pre- and Post-natal Sensitivity

In this document, the potential higher risks for children, compared to adults, were accounted for in part by using estimated exposures by age groups, and by using the higher infant's inhalation rate to calculate the reference concentrations for residents and bystanders. With respect to the toxicology of sulfuryl fluoride, there was no evidence for potential increased sensitivity by infants and children to the prenatal and post-natal toxicity (excluding developmental neurotoxicity, see discussion in the next paragraph) of sulfuryl fluoride. The developmental (**III.G.**) and reproductive (**III.F.**) toxicity studies showed decreased fetal or pup body weight in some studies with NOELs higher than those for maternal effects. For example, the reproductive NOEL was 20 ppm for decreased pup weight while the maternal NOEL was 5 pm for lung lesions (Breslin *et al*., 1992). No teratogenic effects were observed in the developmental toxicity studies (Hanley *et al*., 1980, 1981, and 1989). U.S. EPA concluded that a FQPA factor for this concern was not necessary (U.S. EPA, 2004c).

There is a concern for potential developmental neurotoxicity in humans exposed to sulfuryl fluoride, which caused vacuoles in the adult brain after repeated exposures and in multiple species (Table 16). This concern is consistent with the U.S. EPA weight of evidence for developmental neurotoxicity study considerations, which included: neuropathology, endocrine disruption, behavioral/functional effects, structure-activity-relationship, and neurotoxic potency

(Makris, 1998). The consequence of this vacuolation lesion in the adult is unclear. In majority of the studies, the presence of brain vacuoles occurred without clinical signs (Table 16). In the 2-week mouse study, functional observational battery tests showed no treatment-related effect in the presence of vacuolation in the brain. It is unknown if the same lesion will occur from *in utero* or milk exposure because fetal and pup brains were not examined histologically in the developmental toxicity studies and 2-generation reproductive toxicity study. In the reproductive toxicity study, a comparison of reproductive effects between the F0 and F1 generation did not show any additional reproductive toxicity in the F1 generation, which was exposed to sulfuryl fluoride from *in utero* to adulthood. Results from a developmental neurotoxicity study would provide important information regarding potential effects in the young that are not examined in these developmental and reproductive toxicity studies (U.S. EPA, 1998 and 1999c). However, such a study will not be conducted because the U.S. EPA waived the data requirement in their food use assessment (Dellarco and Baetcke, 2004). The main justification of the waiver was that both chronic dietary exposure and residential inhalation exposures were expected to be relatively low. At the same time, the U.S. EPA indicated that they remained concerned about this effect and retained the 10-fold FQPA database uncertainty factor in the calculation of reference concentrations for chronic dietary and residential exposures. Therefore, this document included an additional 10-fold factor in the reference concentration calculation, and margins of exposure considerations. While DPR prefers to have experimental data to address this concern, this approach expedites the completion of the risk assessment for this compound (Gee, 2004; **Appendix E**). The use of this 10-fold default factor results in uncertainty of the risk estimate, which may be an over- or under-estimation of the actual risk.

V.E.2. Aggregate Exposure

There could be aggregate exposures of sulfuryl fluoride and fluoride from multiple exposure routes and this would be addressed in the dietary risk assessment document for ProFume®. The U.S. EPA conducted an aggregate exposure assessment for sulfuryl fluoride and fluoride from non-food and food sources, and concluded that the risk estimates for both compounds were below the Agency's level of concern (U.S. EPA, 2004a). As a comparison, the inhalation exposure estimates for sulfuryl fluoride in this document (Tables 18 to 23) were much higher (in mg/kg/day to *u*g/kg/day range) than the dietary chronic exposure (1 ng/kg/day to 4 ng/kg/day) estimated by the U.S. EPA.

V.E.3. Cumulative Toxicity

There is a potential for cumulative toxicity of fluoride from sources such as drinking water, cryolite, sulfuryl fluoride, and fluoride supplemented consumer products.

V.E.4. Endocrine Effects

The current database did not show sulfuryl fluoride to cause endocrine disruption effects.

VI. CONCLUSIONS

The human health risk associated with the use of sulfuryl fluoride in structural and non-food commodity fumigation was evaluated in this Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals: neurotoxicity in rats and rabbits for acute, 1-2 week, and subchronic exposures, and lung pathology in rats for chronic exposure. The primary route of exposure was inhalation for workers, residents, and bystanders. Estimated human exposures were evaluated in terms of margins of exposure, and a comparison with the reference concentrations to determine the scenarios of potential health concern. The estimated acute exposures in all bystander scenarios exceeded 1/10 of the reference concentrations, thus would meet the criteria for listing under the AB 1807 Toxic Air Contaminant Act. The MOEs for the following tasks and exposure duration did not meet the benchmark of 100 for occupational exposure or 1000 for residential and bystander exposures:

1. Structural fumigation:
    a. Workers at submaximal application rate: total fumigator activities (chronic), fumigator and tent crew tasks (all durations), ground seam opening (1-2 week, subchronic and chronic), roof seam opening (1-2 week, subchronic and chronic), tarpaulin folding (chronic), and general detarping (all durations).
    b. Workers at maximal application rate: introducing fumigant (1-2 week, subchronic, and chronic), total fumigator activities (1-2 week, subchronic, and chronic), fumigator and tent crew tasks (all durations), and all tent crew activities (all durations).
    c. Residents following clearance: all age groups (acute).
    d. Bystanders during application phase: all age groups (submaximal and maximal rate application, acute 12-hour and 24-hour).
    e. Bystanders during TRAP method of aeration: all age groups (submaximal and maximal rate application, acute 2-hour).
    f. Bystanders during Stack method of aeration: all age groups, except 15-18 years (submaximal rate application, acute 1-hour), and all age groups (submaximal rate application, acute 4-hour; maximal rate application, acute 1-hour and 4-hour).

2. Non-food Commodity fumigation: all bystanders (acute 24-hour).

The potential for health concerns in these scenarios should be viewed in the context of the limitations and uncertainties discussed. The toxicology database, while complete with respect to registration requirements in California, did not include a developmental neurotoxicity study. This study would be helpful to determine the neurotoxicity potential of sulfuryl fluoride in infants and children. The assumption in this Document was that the NOEL would be 10-fold lower than the critical NOELs. Additional acute toxicology studies with shorter observation periods or declining doses could better characterize the potential toxicity associated with some fo the exposure scenarios. Additional exposure data, in particular those with maximal application rate and for commodity fumigation, are needed to better estimate actual exposures. Furthermore, expanded uses such as food commodity fumigation could result in higher exposures and lower margins of exposures. This aspect should be considered in the regulation of this use and future uses.

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VIII. APPENDICES